

TRANSCRIPT OF PROCEEDINGS -7 P1:42

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANEL MEETING

OPEN SESSION - VOLUME I

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Pages 1 through 140

**Gaithersburg, Md.
July 27, 2000**

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANELS

OPEN SESSION - VOLUME I

Thursday, July 27, 2000

10:30 a.m.

Gaithersburg Holiday Inn
Gaithersburg, Maryland 20894

MILLER REPORTING COMPANY, INC.
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P A R T I C I P A N T S

Microbiology Devices Panel Members:

Michael L. Wilson, M.D., Acting Chair

Margaret R. Hammerschlag, M.D.

Valerie L. Ng., Ph.D. M.D.

Carmelita U. Tuazon, M.D.

Melvin P. Weinstein, M.D.

David T. Durack, M.D., Ph.D., Industry Representative

Stanley M. Reynolds, Consumer Representative

Consultants:

Ellen Jo Baron, Ph.D.

Douglas M. Hawkins, Ph.D.

Frederick S. Nolte, Ph.D.

L. Barth Reller, M.D.

Margot A. Smith, M.D.

Steven C. Specter, Ph.D.

John A. Steward, M.D.

Panel Discussants:

Col. Erik A. Henschel, Ph.D.

Richard F. Meyer, Ph.D.

Guest Speaker:

Joseph L. Curtis, Ph.D.

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P R O C E E D I N G S

1
2 DR. WILSON: As the first order of business I
3 would like to turn the meeting over to Ms. Freddie Poole,
4 who will give some general information for all of you.

5 MS. POOLE: Good morning and welcome to this
6 general meeting of the Microbiology Devices Panel.

7 I have some brief information. The audiovisual
8 technicians have asked us to speak directly into the
9 microphone. If you want to come forward to say something,
10 please speak directly into a microphone at the presenters'
11 table that is in front of us. If you have a cell phone or a
12 pager, could you turn it on "vibrate" so that it won't
13 disturb the rest of the speakers or the panel members during
14 deliberations? Thank you, and Dr. Wilson?

15 DR. WILSON: Thank you. As the first order of
16 business here, I would like to have everyone on the panel
17 introduce themselves. I would like to thank all the panel
18 members for being here, as well as the members of the
19 audience and our speakers today. I would like to start with
20 you, Stan, if we could.

Introductions

21
22 MR. REYNOLDS: Good morning. I am Stan Reynolds,
23 Pennsylvania Department of Health, and I am the consumer
24 representative.

25 DR. DURACK: Good morning. I am David Durack. I

1 am the industry representative, just joining the panel, and
2 I am with Becton Dickinson.

3 DR. HAWKINS: Good morning. I am Douglas Hawkins,
4 statistician, University of Minnesota.

5 DR. BARON: I am Ellen Jo Baron, panel member,
6 from Stanford University.

7 DR. SPECTER: I am Steven Specter. I am a panel
8 member, from the University of South Florida College of
9 Medicine.

10 DR. RELLER: Barth Reller, Duke University Medical
11 Center.

12 DR. NG: Valerie Ng, University of California San
13 Francisco.

14 DR. WEINSTEIN: Melvin Weinstein, Robert Wood
15 Johnson Medical School, New Brunswick, New Jersey.

16 DR. WILSON: Again, I am Dr. Michael Wilson,
17 Denver Health Medical Center, University of Colorado School
18 of Medicine.

19 DR. TUAZON: Carmelita Tuazon, from George
20 Washington University Medical Center.

21 DR. HAMMERSCHLAG: Margaret Hammerschlag, from
22 State University of New York Health Science Center, in
23 Brooklyn.

24 DR. STEWARD: John Stewart, from Division of
25 Infectious Diseases, Center for Disease Control, Atlanta.

1 DR. SMITH: Margot Smith, from Washington Hospital
2 Medical Center.

3 DR. NOLTE: Rick Nolte, Emory University, Atlanta,
4 and a member.

5 COL. HENCHAL: I am Col. Erik Henschal, U.S. Army
6 Medical Research Institute of Infectious Diseases.

7 DR. MEYER: Good morning. I am Rich Meyer, from
8 CDC, Bioterrorism Program.

9 DR. GUTMAN: I am Steve Gutman. I am Director of
10 the Division of Clinical Laboratory Devices at the FDA,
11 which is the unit sponsoring this event.

12 DR. WILSON: Thank you and welcome. Now I would
13 like Ms. Poole to read the conflict of interest statement.

14 **Conflict of Interest Statement**

15 MS. POOLE: For the Microbiology Devices Panel
16 meeting, the conflict of interest statement, July 27, 2000:
17 The following announcement addresses conflict of interest
18 issues associated with this meeting and is made part of the
19 record to preclude even the appearance of impropriety.

20 To determine if any conflict existed, the agency
21 reviewed the submitted agenda and all financial interest
22 reported by the committee participants. The conflict of
23 interest statutes prohibit special government employees from
24 participating in matters that could affect their or their
25 employers' financial interests. However, the agency has

1 determined that participation of certain members and
2 consultants, the need for whose services outweighs the
3 potential conflict of interest involved, is in the best
4 interest of the government.

5 For participation in today's discussion all of the
6 panelists have been granted limited waivers for their
7 employment or their financial interest in firms that could
8 potentially be affected by the panel's discussions. This
9 includes Drs. Ellen Baron, Margaret Hammerschlag, Douglas
10 Hawkins, Barth Reller, Valerie Ng, Frederick Nolte, Margot
11 Smith, Steven Specter, John Stewart, Carmelita Tuazon,
12 Melvin Weinstein, Michael Wilson and Mr. Stanley Reynolds.

13 Copies of these waivers may be obtained from the
14 agency's Freedom of Information Office, Room 12A-15 of the
15 Parklawn Building.

16 The agency would also like to take note for the
17 record that Dr. Richard Meyer, who is a guest discussant
18 with us today, has acknowledged that his employer has an
19 interest in developing assays intended to identify biotreat
20 agents or provide evidence of exposure to agents.

21 Col. Erik Henchal, who is a guest speaker with us,
22 has acknowledged that his employer has an interest in the
23 issue to be discussed by the panel. They are also
24 developing assays for military usage.

25 In the event that the discussions involve any

1 other products or firms not already on the agenda for which
2 an FDA participant has a financial interest, the participant
3 should excuse him or herself from such involvement, and the
4 exclusion will be noted for the record.

5 With respect to all other participants, we ask in
6 the interest of fairness that all persons making statements
7 or presentations disclose any current or previous financial
8 involvement with any firm whose products they may wish to
9 comment upon.

10 DR. WILSON: Thank you. The meeting today is an
11 issues meeting where we are going to discuss issues relevant
12 to bioterrorism. The specific issues that we have been
13 asked to address are the appropriate types of important,
14 relevant and reasonable data and information required to
15 assess safety and effectiveness of diagnostic tests that are
16 intended to identify the presence of biothreat agents,
17 specifically when used on different specimen types and under
18 different conditions for evidence of exposure to biothreat
19 agents.

20 This is a topic, as you all know, that has
21 received an enormous amount and appropriate amount of
22 attention in the past few years, and I think that this
23 meeting is one of a series of steps being taken to make sure
24 that the different entities that are working on bioterrorism
25 preparedness are coordinating their efforts.

1 I would like to ask the panel to hold any
2 questions until after all of the presentations this morning,
3 and I would like to remind the audience that only the panel
4 members can ask questions of the speakers.

5 Our first presentation today will be by Dr.
6 Elizabeth Jacobson, who is the Senior Advisor for Science in
7 the Office of the Commissioner of the Food and Drug
8 Administration.

9 **Opening Statement**

10 DR. JACOBSON: Thank you, Dr. Wilson. Good
11 morning, and would like to welcome you all to this very
12 important meeting today.

13 Good science is the foundation for FDA's
14 regulatory decisions, and the focus of today's meeting is
15 very much on science. Unlike most device panel meetings
16 which concentrate on individual applications for marketing a
17 specific device, today we are here to discuss general
18 scientific types of evidence for characterizing assays that,
19 hopefully, we will never have to use widely. These are
20 assays that would be used to identify the presence of
21 biological agents or microbial products that can be used in
22 terrorist attacks, so-called bioterror agents.

23 These bioterror agents are those with a potential
24 to be used intentionally to cause human disease or injury.
25 These are organisms such as Bacillus anthracis, Yersinia

1 pestis, diverse viruses such as equine encephalitis virus
2 and microbial products such as Clostridium botulinum toxin.

3 Obviously, we need to be prepared for such
4 horrific uses of these organisms, and many agencies and
5 organizations are working together to try to ensure that we
6 will be prepared. Today, we want to talk about
7 identification of these organisms in the clinical
8 laboratory. Clearly, the laboratory identification of these
9 agents will be important in almost any scenario that we can
10 envision, and it will be vital to an effective medical
11 response.

12 One critical need of laboratories is diagnostic
13 reagents, reagents and kits to quickly and efficiently
14 determine whether one of these organisms is in a specimen or
15 not. Both CDC and the military are very much involved in
16 assessing these laboratory needs. We would like to
17 especially extend our appreciation to experts from both CDC
18 and DOD who are participating in our meeting today, in
19 particular Col. Erik Henschel who is the Defense Technology
20 Objective Research Coordinator at the U.S. Army's Medical
21 Research Institute of Infectious Diseases at Ft. Detrick,
22 and Dr. Richard Meyer who is Director of the Bioterrorism
23 Rapid Response in Advanced Technology Laboratory at CDC.

24 Many of you in the room today also are working on
25 these challenges in different ways and we appreciate your

1 interest and support in being at the meeting today.

2 As you know, FDA's role is to assure that these
3 diagnostic tests to detect biotreat agents are both safe
4 and effective. In many ways these are not ordinary assays,
5 and assuring their safety and effectiveness presents some
6 unique challenges. The purpose today is to discuss the
7 science of demonstrating the safety and effectiveness of
8 these diagnostic tests in terms of the types of data needed
9 to provide this demonstration. Our job -- the panel, the
10 expert speakers, the audience and FDA -- is to determine
11 what types of data we need to be confident that these tests
12 would actually detect biotech organisms, and how well.

13 To succeed in our task today and, indeed, to
14 succeed in preparing for potential acts of biological or
15 chemical terrorism, we need the cooperation and partnership
16 that we are seeing among medical and public health
17 professionals, emergency management people, the military and
18 law enforcement professionals.

19 I look forward to a most productive meeting today
20 and thank you all very much for being here.

21 DR. WILSON: Thank you, Dr. Jacobson. The next
22 presentation will be by Dr. Steven Gutman, who is the
23 Director for the Division of Clinical Laboratory Devices in
24 the Office of Device Evaluation, in the Centers for Devices
25 and Radiologic Health.

1 devices used to identify biothreat agents in general. We
2 recognize that the validation of such devices presents
3 unique challenges to both scientists and regulators because
4 the clinical specimens needed to characterize these devices
5 may not be readily available and, in fact, may not even be
6 possible to obtain.

7 Our intent is to use today's panel discussion and
8 recommendations to develop guidance for test developers,
9 manufacturers and FDA reviewers on the types of scientific
10 data needed to support device approval.

11 As Dr. Jacobson has already also pointed out, the
12 laboratory plays a critical and pivotal role in bioterrorism
13 preparedness. The laboratory identification of one of these
14 organisms may be the first clue that a bioterrorist event
15 has occurred. The importance of having accurate tests in
16 such circumstances becomes imperative for public health and
17 potentially a matter of life and death.

18 [Slide]

19 Up to now there has been limited commercial
20 incentive for the development and manufacture of these
21 products. Thus, reagents and test kits for the
22 identification of biothreat are not widely available.
23 Products that are available for the identification of these
24 organisms have been developed, and more are under
25 development, by specialty and research laboratories,

1 primarily within the Department of Defense and the CDC.

2 Testing using these products is usually validated
3 within these laboratories, and results from testing with
4 such reagents or kits may be used in clinical management
5 when the testing is performed in these laboratories. These
6 laboratories, in fact, do have an FDA sanctioned name; those
7 are called home brew tests.

8 When CDC or the Department of Defense labs send
9 these same reagents or kits to other laboratories, they are
10 labeled for reference or research use, and not for clinical
11 use. These local labs may then develop and validate their
12 own test using the reagents within their own facility.

13 Because of the urgent public health and national
14 defense need associated with bioterrorism preparedness,
15 these reagents are being distributed and more will be
16 distributed to state and local laboratories. At those
17 laboratories, these products could have a variety of uses,
18 including epidemiologic, forensic and environmental
19 monitoring, and we realize too that these test results from
20 the use of these products could be used for patient
21 management.

22 The question comes up, are we going to rely on
23 investigational products to identify biothreat agents? Yes,
24 we will. These products will have information provided to
25 support scientific soundness of the investigation, and there

1 would be expected to be no evidence to believe that a
2 product would be ineffective.

3 [Slide]

4 At this time, the distribution of these products
5 is primarily occurring through a national laboratory
6 network, and the expectation is that clinical use will be
7 limited to isolated incidents and/or unusual circumstances.
8 However, the potential exists for wider use of these
9 products associated with a large-scale terrorist event or
10 during military operations. FDA believes as bioterrorism
11 initiatives mature and broaden, the laboratory capability to
12 support these programs will also expand. The types of
13 products utilized will most likely become more diverse and
14 versatile, and they are likely to be used in more diverse
15 settings outside of designated laboratories.

16 FDA regulations applicable to manufacturers in the
17 private sector are equally applicable to federal agencies
18 when they take on parallel functions of manufacturing or
19 distributing in vitro diagnostic devices. From a regulatory
20 perspective, these products are investigational devices
21 until their safety and effectiveness is demonstrated and
22 they are cleared or approved by FDA. If they are analyte-
23 specific reagents they need to be in compliance with the
24 analyte-specific reagent rules.

25 [Slide]

1 The level of validation, both analytical and
2 clinical, that is generally expected by FDA depends on
3 intended use and the setting in which the device will be
4 used. For example, products intended for point of care use
5 would have different types of data expected than products
6 used in a clinical laboratory.

7 The reagents and test kits for the identification
8 of biothreat agents would fall into at least four distinct
9 categories based on intended use. That is, tests intended
10 to detect exposure to biothreat agents on samples such as
11 swabs from nasal membranes, skin or hair; tests intended to
12 detect threat agents directly from human specimens prior to
13 culture isolation or without the benefit of culture
14 isolation; tests intended to identify isolates from cultured
15 specimens; and, finally, serologic tests to identify human
16 host response as a marker for infection or immunologic
17 exposure.

18 [Slide]

19 Designing new assays and validating the
20 performance of clinical laboratory assays intended for the
21 identification of biothreat agents pose numerous challenges.
22 Natural infections by these agents are usually rare, and
23 these organisms are rarely recovered in clinical
24 laboratories. The form of disease or infection resulting
25 from deliberate exposure to a large number of organisms may

1 be different from naturally occurring infections. Not all
2 laboratories have the biosafety capability to safely handle
3 these organisms. Banked specimens from infected patients
4 are limited and prospective populations for clinical
5 performance evaluation are generally non-existent. Finally,
6 culture methods may be unreliable or impractical, or the
7 agent may, in fact, not be culturable.

8 Furthermore, there is limited experience with
9 testing for environmental exposure, that is, testing body
10 surfaces to determine contact with the microbial agent
11 likely to cause disease before a patient has been infected
12 or has mounted an immunologic response. For biothreat
13 agents we do not know that aerosols are expected to be the
14 most likely route of transmission.

15 In order to properly assess the performance
16 characteristics of such exposure assays it would be
17 important to know the optimum type of sample to collect, and
18 the length of time an organism is detectable in that sample.
19 Studies intended to gather such information have been done
20 using animal models. There is little information available
21 in the literature regarding exposure to biothreat agents
22 through aerosols, and most of the available information is
23 from DOD published studies.

24 In light of the importance of these test products
25 and the complicated issues involved in characterizing their

1 performance and in determining appropriate use, FDA would
2 like to pose, as a starting point for today's panel
3 discussion, the following questions:

4 [Slide]

5 One, what types of data and information would be
6 considered appropriate to evaluation safety and
7 effectiveness when these assays are used to identify culture
8 isolates from human specimens, or to rule out
9 identification?

10 To test specimens from humans suspected to have
11 infectious processes, in order to identify or detect the
12 agent directly?

13 To test specimens from humans suspected to have
14 been exposed to an agent, or to identify the agent directly
15 in specimens when testing may be performed outside a
16 clinical laboratory?

17 [Slide]

18 Two, to determine or infer effectiveness for these
19 devices, can specimens from naturally or experimentally-
20 infected animals be used when appropriate specimens from
21 humans cannot be obtained? What are the constraints or the
22 limitations for use of animal data as evidence for
23 effectiveness?

24 Three, are there issues not addressed by the
25 described types of data and information that would impact on

1 the reliability of using these assays for evidence of human
2 exposure or infection?

3 I want to reiterate that we are interested in
4 recommendations that can be applicable to a range of agents.
5 We are not asking you to recommend exceptions for these
6 products, and we do not expect you to make specific detailed
7 recommendations but, rather, to provide input on the general
8 types of evidence that could reasonably provide confidence
9 that these products are safe and effective.

10 Generally used approaches are described in several
11 of the background documents provided, including the
12 guidances from NCCLS, the Association for Molecular
13 Pathology and the Association of Official Analytical
14 Chemists. We hope that these have been helpful for
15 outlining approaches for validating performance. Drs.
16 Henschal and Meyer will also give you information about how
17 they have been approaching these validation issues, and we
18 look forward to your thoughts and advice on these important
19 issues.

20 DR. WILSON: Thank you, Dr. Gutman. Our next
21 presentation will be given by Col. Erik Henschal, who is the
22 Defense Technology Objective Research Coordinator for the
23 United States Army Medical Research Institute of Infectious
24 Diseases, or USMRIID, Ft. Detrick, Maryland. Col. Henschal?

25

Panel Discussants

1 COL. HENCHAL: Well, I thank the FDA and the panel
2 for giving me this opportunity to speak today.

3 [Slide]

4 The comments that I am going to give you are my
5 own and have not been endorsed by the DOD. The research
6 program that I am going to describe to you is part of the
7 Joint Service Program that involves not only Army scientists
8 but also Navy and Air Force scientists, some of whom are
9 represented in the audience today.

10 [Slide]

11 The development of medical diagnostics in the
12 Department of Defense is not done in a vacuum. It is part
13 of the total strategy that has been developed, and it
14 interfaces with others in the community for a chem/bio
15 defense. We deal with not only the medical issues of
16 biothreat agents but also with environmental detection and
17 physical countermeasures in particular.

18 [Slide]

19 The problem that we are faced with is that on our
20 battlefield we are not just dealing with biological threat
21 agents. We also have a number of endemic infectious
22 diseases, and one of the things that we want to avoid in the
23 Department of Defense is having developed systems that are
24 just for biological threats and have other systems for
25 endemic disease. So, we have developed a program to address

1 common technologies that could be used to generally address
2 the infectious diseases that might be faced by our service
3 members.

4 [Slide]

5 These are the three patient scenarios that
6 generally we recognize with regard to biological warfare
7 agents. The problem is that if you open up the manual of
8 clinical microbiology you will find out that we do a very
9 great job when the patient is very ill, but that is the
10 point at which we can have the least impact. So, a lot of
11 the research that we are doing within the DOD is to try to
12 push up to the earliest point, and be able to take the
13 threat agent infection at the earliest point after exposure.

14 [Slide]

15 These are some of the clinical specimens that we
16 generally have to collect or that we are recommending
17 collection during the course of disease and shortly after
18 infection. The use of swabs, especially in the post-
19 exposure mode, is not meant to be a triage method but more
20 an epidemiological method to assess generally the exposure
21 that the unit might have been exposed to downwind from an
22 incident.

23 [Slide]

24 We recognize that many of the approaches that we
25 are using have been modernized by the FDA or renewed by the

1 FDA but, at the same time, we try to develop an approach
2 that will give us the maximum confidence in the laboratory
3 result that we obtain.

4 [Slide]

5 In my program, I try to encourage an integrated
6 process so that no technology by itself results in an agent
7 identification in that we actually try to integrate many
8 different technologies, as well as approaches in clinical
9 diagnoses from physician observations in our identification.

10 [Slide]

11 Again, the reason for that is overall to increase
12 confidence in the final result that we have. So, we have a
13 process within the DOD of using screening assays, what we
14 call confirmatory assays that very often are in a theater of
15 operation, and then the definitive identification is left to
16 the reference centers, either the U.S. Army Medical Research
17 Institute of Infectious Diseases or the Navy Medical
18 Research Center, or the Armed Forces Institute of Pathology.

19 Now, whether or not a particular medical
20 countermeasure is used depends upon really the level of
21 confidence that the laboratorian is going to have in the
22 result. We are not requiring necessarily that the response
23 wait for the definitive identification because in a matter
24 of time it is very critical that we know that a particular
25 biological warfare agent is present. So, very often, based

1 on a screening result, commanders may direct that personnel
2 get into protective clothing. But that would not be
3 sufficient to have a medical response such as to give
4 antibiotics to a unit.

5 We generally require that at least two
6 independently derived -- and this is similar to the two-test
7 concept in most laboratories -- we usually require two
8 independently derived markers to be used before any clinical
9 decision is made. This is a practice that has been adopted
10 by many medical commanders. But the strategic decision of
11 how to respond generally to an incident usually awaits the
12 definitive identification.

13 [Slide]

14 The kind of unit that we are primarily dealing
15 with as the first stop for testing many of these approaches
16 is a laboratory such as the 520th Theater Army Medical
17 Laboratory. This happens to be the only active Army
18 deployable laboratory that can operate in a theater. This
19 is a laboratory that has gone to Bosnia, that has gone to
20 Kuwait, Saudi Arabia and will go to Korea.

21 The Navy has similar laboratories worldwide, and
22 the Air Force is developing laboratories that are called
23 Biological Assessment Teams. Most of the technologies that
24 we put into the 520th TAML, as we call it, are very
25 classical methods for which we have high confidence based on

1 historical use at USMRIID. The Navy and Air Force have a
2 similar approach.

3 [Slide]

4 The other laboratory that we have within the DOD
5 and at USMRIID is a special pathogen sample test laboratory.
6 This laboratory first stood up to support the biological
7 warfare convention and the joint sampling protocols, and
8 soon became involved in many of the investigations of bio-
9 warfare threats through 1998 and 1999 with the FBI. It
10 generally operates under a forensic standard and uses the
11 quality systems data guidelines.

12 [Slide]

13 These laboratories have given us and the DOD a
14 great deal of experience in handling a large number of
15 different kinds of specimens, and we are currently
16 transferring that information to the CDC, and you are going
17 to hear more about the laboratory response network, I am
18 sure, from Dr. Rich Meyer. We have a whole series of
19 laboratories of different levels of capability, all tending
20 towards improved confidence in a particular laboratory
21 result. Dr. Meyer will talk more, I am sure, about the
22 different levels.

23 [Slide]

24 But the DOD has a requirement to be able to mount
25 a global response, and one of the things that we find is

1 that the CDC's program is primarily focused on the domestic
2 response. We have, in the DOD, a requirement not only to
3 look at terrorism but the actual use of a weapon of mass
4 destruction on a battlefield. So, we are developing, at
5 least at the grassroots level, a comprehensive system that
6 parallels and uses similar guidelines as the CDC, and
7 certainly we will see that these systems will mature in a
8 parallel fashion with horizontal links where appropriate.

9 [Slide]

10 Certainly, what we have done within the Army, at
11 least, has been to develop what we call these laboratory
12 augmentation packages that we are sharing with our
13 laboratories to prepare for a particular response in case a
14 weapon of mass destruction is used. You will see, again,
15 that a lot of technologies that we are talking about are
16 very mature, but they have not been approved for clinical
17 use by the FDA.

18 [Slide]

19 Just to review some of the basic technologies that
20 have been very successful, such as the immunofluorescence
21 assay -- and I apologize for this figure; it doesn't come
22 out very well on the overhead, but the immunofluorescence
23 assay is a very mature technology that has been around for
24 50 years, and laboratorians have great confidence in it.

25 [Slide]

1 I am sure you are also familiar with the enzyme-
2 linked immunoassay which also is pretty much core technology
3 for DOD laboratories in order to identify agents, and the
4 response of exposed personnel to particular kinds of agents.

5 [Slide]

6 These technologies are now being supplemented by
7 other kinds of approaches, and some of you may be familiar
8 with the immuno-chromatographic assay. This particular
9 assay has been exploited, and the technology has been
10 exploited by my counterparts at the Navy Medical Research
11 Center, and has been used extensively for non-medical
12 considerations. There are commercial efforts that have also
13 developed these tests. You may hear of them as SMART tests
14 or by different names. There has been an attempt to put
15 these in the hands of some first responders. Unfortunately,
16 they have not reached full validation for clinical use.

17 [Slide]

18 This just gives you a quick survey of the
19 threshold sensitivity of many of the approaches. I try to
20 remind people that actually the most sensitive way to detect
21 or identify organisms is usually through classical
22 microbiology. Actually, when laboratorians call me, I
23 remind them that they have the tools generally for many
24 agents, especially the bacterial agent identification, in
25 their own laboratories. Some of the most powerful

1 techniques are in the Manual of Clinical Microbiology.

2 [Slide]

3 This pretty much represents the current strategy
4 for medical diagnostic systems, which is eventually to
5 develop a comprehensive integrated system. That single
6 platform, we believe, will integrate many different kinds of
7 technologies to do agent identification.

8 The first system that the DOD has proposed, or
9 that we have proposed is actually the fielding of a portable
10 rapid nucleic acid analysis system. Eventually, we would
11 like to marry that with improved immunodiagnosics and put
12 that on a single platform for use in our laboratories.

13 [Slide]

14 I am sure you are aware of the many challenges of
15 gene analysis and gene amplification technologies. One of
16 the problems for us is that at each step specimen processing
17 and amplification and detection, all these, represent
18 significant validation challenges before we can license
19 these kits. I think that the panel is going to review some
20 of these products in the future.

21 [Slide]

22 The research goal of the DOD program is pretty
23 much to take advantage of new technology and develop tools
24 for more rapid specimen processing, which really is a
25 fundamental challenge. Each different kind of medical

1 specimen really, right now, requires an independent and
2 unique protocol. There have been many technological
3 advances that are making portable gene amplification and
4 detection more available to the laboratories.

5 [Slide]

6 There are several different commercial, off-the-
7 shelf devices that are becoming available for research use,
8 at least, and I think we are soon going to be seeing these
9 in our clinical laboratories at least in an investigational
10 context.

11 Specimen processing remains still a significant
12 challenge, and there are a number of ways to address this.
13 There are kits that are available, commercial kits that are
14 available for processing whole blood. Some of these have
15 evolved especially in the HIV program, and there are new
16 methods for rapidly purifying DNA.

17 [Slide]

18 In addition, there are devices in our program for
19 processing blood in five to ten minutes that have been able
20 to give us reasonable sensitivity. Experiments at USMRIID
21 have shown that our target sensitivity really is within the
22 range of 100-1000 colony-forming units for anthracis in a
23 medical specimen. That gives us the needed sensitivity to
24 detect a post-exposure event.

25 [Slide]

1 We have also decided pretty much on some common
2 gene amplification chemistry. This is proprietary
3 chemistry. The advantage has been that the DOD scientists
4 at AFIP, at the U.S. Air Force Epidemiological Service, at
5 the Navy and at USMRIID have been able to develop assays for
6 over 26 agents. So, if you were looking for a common gene
7 amplification technology, this is it. Of course, it is
8 going to be almost a lifetime of work in order to be able to
9 validate all of these assays so that they are acceptable for
10 human clinical laboratories.

11 [Slide]

12 One of the things we are also doing within the DOD
13 is that we don't just depend upon "onesies and twosies."
14 What we are trying to do is actually build reagents and
15 processes that actually have diversity and depth.

16 We recognize that the threats of the future aren't
17 the classical threats of 25 years ago, and very often you
18 will hear about the classical threats -- anthrax, plague, Q-
19 fever. In fact, now that we have a proliferation of
20 molecular biology and gene engineering techniques around the
21 world, we know that the next threat is going to be
22 genetically engineered. It is going to contain unique
23 elements such as antibiotic resistance that we were
24 unprepared to look for before. So, in order to avoid that
25 technological surprise, most reagents to date have actually

1 been at the top of the pyramid and the research program that
2 we have in the DOD is to continue to broaden those reagents
3 so that we can dependently detect or recognize infection at
4 the earliest stage.

5 [Slide]

6 This is a variety of tools that are being
7 developed within the DOD. These devices, especially the
8 ones at the top, are rapid core nucleic acid devices that
9 have been placed into boxes or cases that can meet the
10 standard of the DOD. There are other options also being
11 developed and evaluated in the program that will assist us
12 in rapid gene amplification by our field units.

13 [Slide]

14 But we continue to look at methods that can
15 improve immunodiagnosis. I don't want you to think that the
16 problem is just nucleic acid because we also recognize that
17 nucleic acid analysis by itself is not going to help us to
18 detect the non-replicating agents such as some of the
19 purified toxins that are also part of our threat.

20 [Slide]

21 So, we need to continue to look at technologies
22 that can sensitively detect antigens, and both
23 electrochemiluminescence and time-resolved fluorescence are
24 potential methods to detect these antigens in less than the
25 picogram range.

1 [Slide]

2 I am going through these technologies very quickly
3 and if anyone has any questions they can talk to me later
4 about these. Primarily the topic today is about what
5 studies are needed, and we pretty much recognize within the
6 DOD that we have to meet the guidelines that are published
7 by the FDA and the NCCLS guidelines.

8 These are probably the most important studies that
9 I think about at USMRIID, which is to determine the
10 sensitivity and specificity precision, and we are especially
11 concerned about what is going to happen when you have inter-
12 operator, inter-laboratory reproducibility. And, the
13 challenge for all of us is to be able to have these
14 performance characteristics for each indication for each
15 specimen and for each agent. You can imagine that this is,
16 again, a lifetime task.

17 [Slide]

18 Here are the evaluation trials that we are
19 proposing at USMRIID. There are four. We have laboratory
20 studies. We have animal models. We have field-based
21 studies and we have hospital-based studies.

22 [Slide]

23 The laboratory-based studies are primarily used to
24 establish the analytical characteristics of these
25 approaches. Before we can even start we have to establish

1 the controls. There are no international controls for most
2 of these agents. So, we have been investing a great deal of
3 time in trying to establish controls that can be used to
4 compare the performance of different tests.

5 [Slide]

6 We have been doing that through a system of
7 proposed model systems, and these are some of those. One of
8 the things that we are trying to do is to collect sufficient
9 information so that we can select what the best technologies
10 are. We do that through these model systems. I want you to
11 notice that we are looking at both representative biological
12 warfare agents as well as endemic infectious diseases.

13 [Slide]

14 Based on these model systems which will be pretty
15 much the pathfinders for the rest of our development --
16 based on these model systems we have been developing the
17 reference collections that will be necessary in order to
18 evaluate these technologies. So, there are similar
19 reference panels that are being developed for the viruses
20 and toxins.

21 The current bacterial reference collection at
22 USMRIID is about 418 bacterial strains. It includes not
23 only strains that are related to the threat agents
24 genetically, but also includes those that we call the
25 proximity neighbors, those bacteria that are going to be at

1 the same site of our samplings. The most important thing
2 that we have had to do is to extensively characterize these
3 strains using some very well established methods based on
4 the genetics of the organisms, the biochemistry and fatty
5 acid profiles, antibiotic sensitivity and antigenic
6 biomarkers to document the pedigree and strain history, and
7 also an important characteristic is whether or not the
8 agents have documented virions.

9 Some of these activities were originally done
10 through the ATCC. I think you are aware that it has been
11 very difficult to continue to get certified strains from
12 commercial sources. So, it has been pretty much left up to
13 the DOD laboratories in order to establish these collections
14 and do the characterization.

15 [Slide]

16 Within our laboratories, we pretty much have what
17 we call the specimen hierarchy. Most of the original
18 development actually will be done and the tests evaluated
19 using these control materials that have come out of the
20 reference collection.

21 We usually proceed then to the mock specimens,
22 that is doping in an agent into representative clinical or
23 normal clinical specimens. We also have available to us
24 animal specimens. A lot of these were originally from
25 retrospective collections but we are also at the same time

1 now, at USMRIID, doing live challenges especially to look
2 for markers that are important for the early recognition of
3 disease.

4 [Slide]

5 This just shows you the kind of studies that we
6 do. This is the comparison of two different kinds of
7 platforms using a gene amplification method. In this case,
8 the basic chemistries were comparable but this is just an
9 example of the kind of data that we are developing.

10 [Slide]

11 With regard to animal models, I think we know that
12 we are not going to be able to have sufficient human
13 populations to do the classical validation for infectious
14 disease. So, it is very important to use some of the
15 established animal models that we have had at USMRIID, that
16 were developed at USMRIID over the last 25 years. It is
17 using these animal models that we can establish some range
18 values, where we can look by using blinded panels to
19 determine the clinical sensitivity and specificity of our
20 assays. The intent for future studies will be to use both
21 retrospectively and prospectively collected specimens.

22 [Slide]

23 Field studies -- the purpose of the field studies
24 is really paramount for the DOD to make sure that the new
25 technologies are compatible with the mission requirements.

1 This is a training center that we established at USMRIID for
2 the Theater Army Medical Laboratory. Now it has become a
3 DOD resource for evaluating new diagnostic assays. Most of
4 the issues over here are user friendliness and whether or
5 not the military can support these logistically and from a
6 training standpoint.

7 [Slide]

8 The services are also beginning to introduce some
9 of these approaches to the hospitals in an investigational
10 sense, and this work is just beginning. We have a pilot
11 program at the Brooke Army Medical Center. The Air Force
12 has a similar program that they are developing. The Navy is
13 working with their environmental and preventative medicine
14 units to be able to respond.

15 Our intent is to be able to put these into a
16 CLIA88 laboratory and use a process of centralized IRB
17 review and informed consent in order to get these into our
18 hospitals. We are especially interested in overall
19 improvement of the training base and experience with these
20 assays at the clinical-laboratory level because, again, very
21 often the laboratorians are not familiar with the general
22 process.

23 [Slide]

24 That pretty much summarizes what the current DOD
25 program is. We are hoping that we are going to receive your

1 guidance on how we should best proceed with future
2 validation trials in order to protect the health of our
3 service members in the future. Thank you.

4 DR. WILSON: Thank you, Dr. Henchal. Our next
5 presentation will be by Dr. Richard Meyer, who is the
6 Laboratory Director for the Bioterrorism Rapid Response and
7 Advanced Technology Laboratory for the National Center for
8 Infectious Diseases at the CDC.

9 DR. MEYER: Good morning. I am happy to be here
10 today to talk about our efforts at CDC in conjunction with a
11 number of federal partners in the public health preparedness
12 for potential bioterrorism.

13 [Slide]

14 I will give you a little bit of background
15 information. The program at CDC came about just a little
16 over a year ago, when the Congress of the United States
17 charged CDC with preparing for the public health response in
18 preparedness. We have set up a program at CDC which
19 consists of epidemiological investigations and studies, as
20 well as laboratory capacity and basically building upon
21 laboratory capacity. For a number of these agents of
22 concern in bioterrorism, CDC had not for quite a long time
23 had capacity in this area. A case in point would be
24 Bacillus anthracis.

25 So, number one was the building of laboratory

1 capacity within CDC to strengthen that and, secondly, to
2 establish a laboratory response network which CDC, in
3 conjunction with other partners, for building resources and
4 building capacity basically in the state public health
5 laboratories. So, as a result of this, there has been a
6 support of roughly about fifty, give or take, public health
7 laboratories around the country where we have helped build
8 capacity for the laboratory detection of these biothreat
9 agents.

10 As Col. Henchal mentioned previously, this has
11 been set up initially in a tier system. Laboratories are
12 designated A, B, C and D depending upon their capacity.
13 They are self-identified into the system based upon their
14 particular facilities and what capacities they have for the
15 various agents. We are building upon that to increase the
16 capacity in these laboratories and the eventual goal is to
17 have the laboratories come up to the highest level to be
18 able to have the capacity to test for as many agents using
19 the technologies that we plan to have out.

20 The network has a password protected website. It
21 is coordinated through the American Public Health Laboratory
22 Association. There has been input from our other federal
23 partners, particularly FBI, the DOD, USMRIID, the Navy
24 Medical Research Center, the Air Force and so forth. So, it
25 is a consorted effort among a number of government

1 facilities to combine resources and to increase the public
2 health capacity to deal with bioterrorism.

3 At present time there are assay protocols for a
4 select number of agents that are available at this website.
5 The participating laboratories are able to assess those
6 protocols and also to order reagents directly on the website
7 to perform the laboratory analysis. The assays that are
8 presently available are basically conventional
9 microbiological assays. Again, they have been contributed
10 by subject matter experts both within CDC and outside of CDC
11 such as our partners in DOD, USMRIID and the Navy and the
12 Air Force.

13 What we are doing within CDC to build capacity is
14 the establishment of my laboratory, which is the core
15 bioterrorism laboratory within CDC. We work hand in hand
16 with our other federal partners and also with our divisional
17 specialty laboratories within CDC. So, we are a rapid
18 identification lab. When specimens come to us they are
19 considered unknown and we come up with a rapid of
20 identification of the agent and then triage that to
21 appropriate specialty laboratories.

22 In addition, we evaluate new technologies and we
23 also are in the procedure of developing assays based upon
24 primarily two formats, as you see here, the molecular assays
25 and the antigen detection assays using time-resolved

1 fluorescence. These are the two main formats that we are
2 focusing on, and we hope to have assays that are developed
3 and validated in both of these formats for each of the BT
4 agents of concern and then disseminate them to our
5 laboratory response network.

6 Again, this has been a concerted effort. On the
7 molecular assay development we have a major program going on
8 in conjunction with the Department of Energy, national
9 laboratories, particularly Lawrence Livermore lab, bringing
10 in all of the resources of the DOE and national
11 laboratories. It has been a wonderful collaboration and has
12 helped us quite a bit, as well as the input from our DOD
13 partners and also law enforcement partners. So, it has been
14 a wonderful collaboration of federal agencies coming
15 together.

16 [Slide]

17 The rest of my presentation is going to be very
18 focused on exactly what we are doing for assay development,
19 evaluation and validation. The assays that we are
20 developing on both these formats are intended for
21 dissemination to the laboratory response network and to be
22 available to the user community. We are planning to have
23 these assays available to all of the people that need to
24 utilize these assays, and have the appropriate reagents
25 produced in quantity to make these assays work.

1 [Slide]

2 So, what is our assay development and validation?

3 The objective is to provide assays to public health for
4 detection and identification of possible BT pathogens. We
5 want very rigorously screened assays to ensure selectivity
6 and sensitivity, optimize on the appropriate
7 instrumentation, validated through an inter-laboratory
8 exercise, and then disseminated to the laboratories that
9 need to utilize these assays.

10 [Slide]

11 So, again, what the CDC needs is assays that use
12 targets that are highly specific, utilizing a panel of
13 reagents for each organism as opposed to utilizing just one
14 reagent or target. It must be coupled with sample
15 preparation protocols for a number of different sample
16 types. As Col. Henchal mentioned earlier, this is a very
17 important area. We are not just developing an assay; we are
18 developing a total assay which includes sample preparation
19 from a specified sample type, plugged into the assay and
20 ending up with a final result from start to finish. Most
21 importantly, these assays must be reproducible for all the
22 users.

23 [Slide]

24 Before I get into our actual plan, I would like to
25 go over a couple of terms and our definitions for what we

1 are calling this. Screening and verification is the process
2 by which the primer/probe sets are rigorously evaluated
3 against different DNAs, processes by which antibody pairs
4 are evaluated against different organisms. That is our
5 screening and verification criteria.

6 Validation includes the multicenter collaborative
7 study by which proposed methods are assessed through
8 independent testing and separate laboratories under
9 identical conditions.

10 The standardized assay, the final goal, has a
11 defined sample type, sample preparation method, detection
12 assay and instrumentation. Again, this is our final
13 packaged assay from start to finish.

14 [Slide]

15 So, the first part of this is that assay
16 evaluation is what we do in-house. This encompasses
17 basically two different areas: specificity, no homology; no
18 homology with genetic near neighbors, agents causing similar
19 clinical symptoms, nucleic acids, animal species nucleic
20 acids, nucleic acids from various soil backgrounds and other
21 agents being tested for. Our sensitivity goal is simply what
22 is the lowest number of agents that we can detect with
23 confidence?

24 [Slide]

25 This is our road map to the molecular assay

1 development. It basically begins with the candidate unique
2 genomic regions that are identified for each of the BT
3 agents. That is followed by computer screening of those
4 sequences against a very large database of sequences;
5 followed by wet-chemistry screening of those particular
6 primer sequences that have been identified. That is then
7 plugged into assay development. The assays that look
8 promising are then put into assay validation, again, meaning
9 that they are rigorously screened against a large panel for
10 the background material, as well as a large panel of the
11 specific strain or target organism that we are preparing
12 these assays for. Finally, the assay dissemination.

13 [Slide]

14 On the antigen assay development process we are
15 basically doing the same types of thing. Candidate antibody
16 pairs are screened against specific target organisms. These
17 specific antibody pairs are screened against background
18 organisms. We optimize the antigen detection assays. We go
19 into our validation and then disseminate those assays.

20 [Slide]

21 To give you an idea of our overall plan for assay
22 validation through a multicenter collaborative study, this
23 is an organized collaborative multicenter validation
24 exercise. This is prepared at one site. That identified
25 site will prepare all of the material needed for running the

1 assay, disseminate that to the participating laboratories,
2 collect the results and evaluate and, if we then feel that
3 it meets our requirements, we go on to dissemination and
4 finally FDA approval. If we find that it does not meet our
5 requirements, we go back and re-optimize.

6 [Slide]

7 A little more specifically on the multicenter
8 collaborative study validation exercise, we are utilizing a
9 protocol format which is well established and is part of the
10 AOAC -- American Association of Analytical Chemists, which
11 is an official compendium that FDA utilizes themselves in
12 their own laboratories for various testing. This is a well
13 established, recognized format and we feel it works very
14 well for the assays that we are developing, evaluating and
15 validating.

16 So, for each study we plan to have between five to
17 ten laboratories selected to represent the user community.
18 These will be public health laboratories, military
19 laboratories, FBI, law enforcement, and veterinary
20 laboratories. The package is sent to each lab. It includes
21 identical specimens, identical reagents and standardized
22 assay protocols for extraction and detection. The test is
23 conducted by the laboratories and the data sent back to CDC
24 for analysis.

25 [Slide]

1 What we are looking for in this collaborative
2 multicenter validation is to meet all of these requirements.
3 All of these requirements must be met for us to feel that we
4 have a validated assay that is worthwhile disseminating and
5 can stand up to the criteria for FDA approval.

6 [Slide]

7 In summary, we are working on highly selective
8 screening to develop very robust assays. The results will
9 be validated in a multicenter collaborative study, and this
10 program is designed to provide assays for the widespread
11 community use.

12 We have a number of assays right now which are
13 ready for multicenter validation studies, both molecular
14 assays as well as time-resolved fluorescence antigen
15 detection assays. We are hoping that you coming here today
16 and meeting with you all would be on the right track in
17 doing the types of things, and are looking for
18 recommendations from this expert panel so that we can meet
19 the goals that we have planned.

20 Again, I would like to thank all our partners that
21 are involved in this. It is truly a collection of resources
22 from a number of organizations that have been very, very
23 helpful to us. Thank you very much.

24 DR. WILSON: Thank you, Dr. Meyer. At this point
25 I would like to invite the panel to ask questions of any of

1 our speakers today. Dr. Nolte?

2 DR. NOLTE: I have a question for both the
3 speakers, from CDC and the Army. The issue of quantitation
4 hasn't come up. Is that being addressed in any sort of way
5 as part of the development plans for the assays?

6 COL. HENCHAL: From our standpoint, the
7 qualitative result is more important right now -- whether or
8 not the agent is present, yes or no. For most diseases that
9 we are talking about, quantitative amounts of organisms in
10 the specimen don't really have a role in the clinical
11 diagnosis as far as I know.

12 DR. MEYER: We have the same opinion. Basically
13 we are interested, at least initially, simply in is the
14 organism present or not.

15 DR. NOLTE: But don't you think it might have a
16 role in terms of assessing the nature of the threat and
17 perhaps distinguishing background from a true weapon, if you
18 will, in an area where the organism might be endemic?

19 COL. HENCHAL: That actually might have greater
20 impact when we talk about environmental detection. Most of
21 the threat agents don't appear naturally in human specimens.
22 So, their presence is already an indication of a possible
23 infection.

24 DR. WILSON: Dr. Durack?

25 DR. DURACK: Col. Henschal, you mentioned the

1 importance of high sensitivity, which I am sure we would all
2 agree with, for these tests. But I wonder if you could
3 comment on the issue of false positives. The reason I ask
4 is that in a traditional sensitivity/specificity tradeoff,
5 for a patient who might have an infection the cost of a
6 false positive is usually something like unnecessary
7 treatment or opportunity cost of a missed diagnosis. In
8 this case, of course, the additional cost could be enormous
9 social anxiety, disruption, civil problems, etc. So, we
10 have a tension there that perhaps you could comment on.

11 COL. HENCHAL: Well, every test is going to have a
12 certain level of false positives occurring. No test is
13 perfect. I think we understand that. First, the DOD
14 approach is to overlap as many technologies and approaches
15 as possible to decrease the impact of having that false
16 positive.

17 If you remember my presentation, we talked about
18 the DOD going through a process of having screening results,
19 confirmatory results and definitive identification at the
20 reference centers. So, we try to avoid the impact of false
21 positives by using this process of having a screening result
22 and a confirmed result, and this would be very similar to
23 what is used in other diseases. You remember what has been
24 a paradigm for HIV, for example, to use ELISA and Western
25 Blot, and certainly we are going to employ the same methods.

1 But it is very important to understand that for
2 the diseases that we are talking about, especially anthrax,
3 plague and possibly Variola or small pox, medical
4 countermeasures have to be employed as soon as we can. From
5 the standpoint of a response, it may be necessary to begin
6 some treatments even on the least amount of information so
7 that we can protect health and public safety as soon as
8 possible. I can imagine though that as the independent
9 biomarkers -- as the identification becomes more definitive,
10 then that is the point at which we can better tailor the
11 medical response after an event.

12 DR. DURACK: Thank you.

13 DR. WILSON: Dr. Baron?

14 DR. BARON: I am not certain to whom to direct
15 this question, but I think maybe, Dr. Meyer, you were
16 talking about developing tests that will be available for
17 laboratories. Did that include laboratories that are not
18 public health laboratories, such as hospital or clinical
19 laboratories as well once they have been FDA approved?

20 DR. MEYER: I am talking about tests that will be
21 available to laboratories that are part of the laboratory
22 response network for bioterrorism.

23 DR. BARON And, at the very base level of that
24 response network are initial intake type laboratories, such
25 as hospital or clinical laboratories, isn't that correct?

1 DR. MEYER: Hospital laboratories are classified
2 under our system right now as level A laboratories.
3 Basically, what they do is rule out an agent. At some point
4 in time they might get to a point of elevating from that
5 status. There are some select hospital laboratories around
6 the country, for example Mayo Clinic, that have come into
7 our network at a higher level because they have specific
8 needs for that. So, at least initially those hospital
9 laboratories will be doing basically rule-out and not these
10 types of tests. Later on, down the road that might change.

11 DR. BARON: The reason I am asking that question
12 is because your evaluation process includes public health
13 laboratories but not a lower level or clinical laboratory,
14 and I think that might have some bearing on that process.

15 DR. MEYER: True.

16 COL. HENCHAL: I should mention that it is very
17 likely that the assays that we are developing, the DOD
18 system, will be placed at the first level of definitive
19 care, especially in a battlefield. The Army medical
20 department center and school has asked that these assays be
21 placed at the combat support hospital level, and it is very
22 likely that the bulk of the reference assays may be in what
23 we call a theater reference center, such as the TAML, in
24 order to provide a second level of confirmation of the assay
25 results.

1 DR. WILSON: Dr. Reller?

2 DR. RELLER: To follow up on Dr. Baron's question,
3 could either of you clarify a bit more at what point -- not
4 that they are mutually exclusive, but at what point do you
5 want to detect things? These level B, C reference
6 laboratories are fine when one has, you know, patients with
7 disease resulting from exposure but if one is looking for
8 detection of exposed individuals, then the front line
9 laboratories become very important in the process if the
10 diagnostic efforts are there and where the emphasis would be
11 on extreme sensitivity to rule something out, and to put the
12 public or community at rest when there is a question, and
13 then all of the things that are generated if there is
14 evidence of exposure apart from disease.

15 COL. HENCHAL: Yes, we recognize that there are
16 two cases in which these assays may have to be used. One is
17 in the announced attack, and the announced attack would be
18 the actual event of a terrorist attack or use of a weapon of
19 mass destruction. We can imagine that our preventative
20 medicine units would use some of these tools to evaluate
21 when units have been exposed to an agent and swab sampling
22 might be an important part of that, as well as the use of
23 epidemiological data.

24 In the domestic public health arena this is
25 probably the most important concern, actually the

1 unannounced attack where suddenly large numbers of patients
2 begin appearing at physician offices and emergency rooms,
3 and these are perhaps going to be the most difficult cases
4 to recognize quickly. We only have to refer back to the
5 West Nile virus outbreak of last year to realize the delay
6 that sometimes can occur when you have an unusual outbreak.

7 So, I think the CDC is building actually a
8 comprehensive system to be able to attempt to integrate
9 information from different sources in order to rapidly
10 identify unusual outbreaks of disease.

11 But I want to stress that, you know, ultimately it
12 is going to be the clinical laboratorian that is going to
13 have to recognize when he has analytical questions come up
14 that are not ordinary, in the ordinary scope of his duties,
15 and this is going to require a certain change in how people
16 are trained, and we have to be able to give them the right
17 tools in order to make those decisions in the laboratory.

18 DR. RELLER: But the approaches you have mentioned
19 so far -- it comes back to Dr. Baron's question again, I
20 mean, are you developing for this purpose or not for this
21 purpose? If so, realizing we are not to dwell on a specific
22 agent, but I was intrigued by the listing of the specimens
23 under consideration and if it is exposure or even diagnosis,
24 as far as that goes, but especially exposure for any of the
25 more commonly considered plausible agents, based on damage

1 with methods of delivery, what is the evidence that a swab
2 of mucous membrane, a swab of the skin or a hair sample
3 provides sensitivity for the early detection of exposure to
4 some of the main ones on the list?

5 COL. HENCHAL: Thank you for that question.
6 Actually, what should have been provided to you and the
7 other panel members is actually some at least preliminary
8 studies that were done at USMRIID that showed that swab
9 sampling of the nose, the face and hairy portions of the
10 face can recover Bacillus anthracis at least in the
11 immediate post-exposure period, within 24 hours. We are
12 continuing those studies. We are showing that you can use
13 swab sampling now up to 48 hours using the more sensitive
14 gene amplification technologies. In addition, we are trying
15 to define a whole hierarchy of specimens that can be
16 collected. For example, we have shown that feces is a good
17 sources of spore material 48 hours after exposure.

18 So, a lot of the information you are asking for is
19 currently part of an active research program. There is some
20 data that exists from the older programs that existed in the
21 '60s. We are currently evaluating those. But that is part
22 of our program, to be able to define what are the best
23 technologies that can be used to detect agents at the
24 earliest point after exposure.

25 DR. MEYER: Certainly as Col. Henschal has

1 mentioned, we are very much dependent upon the work that
2 they are conducting to come up with this information. Our
3 focus right now is on just the conventional clinical
4 specimens that one would be testing.

5 DR. RELLER: It becomes also very much a part of
6 Dr. Nolte's query about the quantitation, not so much that
7 quantitation whether it is or not but what one is able to
8 detect on these samples that are markers for exposure, if
9 you have the data in hand that shows that that is true,
10 relative to natural events that have occurred in terms of
11 what the exposure is, what the numbers of, for example,
12 spores are that result in actual disease, and you are
13 talking about what the deposition is in various spots that
14 one could detect as a marker of exposure that should be
15 there under normal circumstances.

16 COL. HENCHAL: Right. I apologize if I de-
17 emphasized the need for quantitative results. Certainly,
18 all of our assays are being evaluated using standard curves,
19 and we are trying to evaluate the range that is necessary
20 for the detection. It has been part of the process. So, it
21 is not just a qualitative result that we are actually
22 developing data for; there is quantitative. But the
23 ultimate test -- the most useful use of the assay will be
24 qualitative, whether or not the agent is actually present or
25 not, to confirm at least a clinician's initial diagnosis.

1 DR. WILSON: Mr. Reynolds?

2 MR. REYNOLDS: Dr. Meyer, just clarify something
3 for me. These kits and reagents that you envision being
4 produced, are they going to be produced solely by CDC and
5 DOD, or do you envision commercial laboratories producing
6 them as well?

7 DR. MEYER: The answer to your question is yes.

8 DR. WILSON: Dr. Hawkins?

9 DR. HAWKINS: Just a follow up to Col. Henschal's
10 comment, when we are assessing the portability of an assay
11 from one laboratory to another. I assume that will be done
12 on the underlying quantitative measure rather than just the
13 yes/no issue, whether it is to the left or to the right of
14 the cut point.

15 COL. HENCHAL: Yes, that is an excellent point and
16 thank you for that.

17 DR. WILSON: Dr. Nolte?

18 DR. NOLTE: I guess since I started this
19 quantitation thing, I will follow up with it. The
20 analytical versus clinical sensitivity that might be
21 required -- I mean, I realize that one of these organisms is
22 often enough to do damage, but just having the knowledge --
23 I mean, if you are talking about assay design, what
24 knowledge base is there in terms of the required clinical
25 sensitivity? Of course, we would like all the assays to be

1 sensitive to a single copy or a single organism but that is
2 not realistic in many cases. Is there any background on
3 that?

4 COL. HENCHAL: Of course, we know the infectious
5 dose for all of the agents, and that is available through
6 the scientific literature. The experiments that we have
7 done with Bacillus anthracis suggest that if we can have
8 assays that are sensitivity in the range 10 to 1000 colony-
9 forming units, we should be able to detect infection in the
10 first 24 hours after exposure.

11 The data that we have is mostly from animal
12 studies. We also know a certain amount, for example, what
13 is the predicted level of bacteremia for anthracis, plague
14 or some of the other agents. So, I am pretty comfortable in
15 reporting that if we can detect as low as 10 to 100 colony-
16 forming units we will be in a very early stage of disease.
17 The problem with anthracis though is that once you detect it
18 in the blood, especially in the animals, the prognosis of
19 the animal is very poor at that point.

20 So, we have to look for other sites to sample in
21 order to actually detect an earlier recognition of disease.
22 But it is also one of the reasons why we are developing
23 assays that look for common pathogenic markers and also look
24 for host response markers. Those are going to be additional
25 pieces of information for persons actually infected. Many

1 of the viruses can infect at the level of one to ten
2 particle-forming units. So, that is going to be the extreme
3 level of our detection, I am sure. I hope that answers your
4 question.

5 DR. HAWKINS: Yes, thank you.

6 DR. WILSON: Dr. Baron?

7 DR. BARON: I notice that you are focusing your
8 host response on antigen detection, but some of the work
9 that is being done, at least around our university, is using
10 up our regulated human cellular proteins that are assayed on
11 biochips, for example, looking at response to infection.

12 COL. HENCHAL: Actually, in our program we are
13 actually concentrating at looking at the transcriptional
14 products of the host response. We have an extensive program
15 in the DOD using microrays right now to evaluation that
16 response. I am happy to report that in the program we have
17 developed a number of different assays, at least for the
18 non-human primates, so that we can at least gain some
19 information from animal studies on one of the most important
20 host response immune markers that could be incorporated into
21 our assays, and these assays are currently being put on the
22 rapid nucleic acid analysis devices. Of course, there
23 already are established immunoassays, ELISA-based assays for
24 detection of different cytokines and chemokines, and these
25 are being used in our hands as gold standards. Rich, is

1 there anything comparable at CDC for looking at host
2 markers?

3 DR. MEYER: Yes, there is a comment on that. I
4 just want to clarify some points. That is, number one, what
5 we are doing in my laboratory is basically very
6 straightforward. We are developing and validating rapid
7 tests that can be used by the user community, laboratory
8 network people so they have a tool to rapidly assess whether
9 there is or is not a presence of a particular organism in a
10 clinical specimen. These are not primarily stand-alone.
11 This is coupled with a slew of information, as Col. Henchal
12 mentioned before. There is epidemiological information,
13 clinical information, and other tests that go along with
14 that to make the final determination of exposure or not.
15 So, there is work in these other areas that is going on, and
16 there is work going on at CDC in those areas by our
17 specialty laboratories and divisions.

18 DR. WILSON: Dr. Nolte?

19 DR. NOLTE: I guess I would like some
20 clarification from the chairman or by the FDA. This bring
21 up an interesting point, if you are looking at human gene
22 expression analysis as a diagnostic adjunct to an infectious
23 disease, is that part of what we are here to talk about or
24 think about?

25 DR. GUTMAN: Well, we certainly didn't imagine

1 that popping up on the table but it is certainly not
2 precluded if you think it would be worthwhile. I am not
3 sure that is what we had in mind.

4 DR. NOLTE: Yes, I mean, it does bring up a whole
5 other level of verification, validation and testing.

6 DR. GUTMAN: The agency, actually, is quite
7 interested in that particular type of technology. I don't
8 think we have discussed it in this context. We have an
9 internal ongoing, actually fairly significant educational
10 program to look at that technology, and there has been some
11 preliminary discussion about whether a new alternative,
12 either scientific or regulatory approaches, would apply to
13 that technology. Again, I wouldn't necessarily take that
14 off the table, but certainly I wouldn't make that central to
15 today's discussion.

16 COL. HENCHAL: Thank you.

17 [Laughter]

18 DR. WILSON: Dr. Durack?

19 DR. DURACK: Dr. Meyer, in follow up to Mr.

20 Reynolds' question about possible involvement of commercial
21 labs, in one of your later slides you said that the program
22 was designed to provide assays for widespread community use.
23 With that in mind, I wonder if you could just make a general
24 comment. If you think about the long trail of development
25 of an assay, do you have a strategy or a philosophy about at

1 what time you would involve industrial collaboration or
2 partners in that process?

3 DR. MEYER: Well, when you say industrial
4 collaboration, can you define that? Are you talking about
5 production, a commercial enterprise producing reagents, or
6 are you talking about those types of establishments
7 participating in the study?

8 DR. DURACK: I was just thinking about the process
9 of product development from the earliest stage to
10 manufacturing. I wondered if you had a strategy or whether
11 you had an approach for your program at the development
12 stage, at the testing stage, at the manufacturing stage.

13 DR. MEYER: Well, first of all, we are using
14 instrumentation and technology that is out there and
15 companies are responsible for, and those commercial
16 enterprises are supporting the work that we are doing for
17 assay development. That is the first thing.

18 Secondly, the assays that we are developing are
19 for the user community. To define user community, it is
20 basically for our laboratory response network and open to
21 the other users or other federal partners in DOD, law
22 enforcement and so forth. I see this as a sharing. Are
23 these assays going to be sent out then to the general
24 public? At this point, that is not the intention.

25 DR. DURACK: Thank you.

1 DR. WILSON: Dr. Baron?

2 DR. BARON: To go to the very lowest, mundane
3 level of question, if my laboratory were to isolate an
4 organism that we thought might be a Bacillus anthracis today
5 and we had no way of really identifying it fully, the
6 biggest problem I would have is how to get it to the state
7 laboratory, except by overnight express mail for another
8 whole day. Have you looked at that level of the problem?

9 DR. MEYER: Well, just to comment on that, yes,
10 there are two ways that this will happen and, of course, it
11 depends on the scenario. If there is a suspicion of a
12 bioterrorist event, law enforcement, particularly FBI, is in
13 charge of that scenario and they come in. They do a risk
14 assessment. If they feel the risk is high enough that this
15 could be real, they will physically bring that specimen to
16 whatever institution they plug into.

17 Secondly, if the risk is low, those specimens will
18 be sent by commercial courier, just the way other types of
19 specimens are sent.

20 MR. REYNOLDS: If I could just comment on that, I
21 have been involved in a series of training exercises for
22 bioterrorism. We have a protocol set up in Pennsylvania
23 where if someone has something that is really suspicious the
24 state police will courier it to us immediately. You know,
25 by helicopter and state police we would get the specimen

1 within hours.

2 DR. WILSON: Are there any further questions? If
3 not, I would like to move now to the open public hearing
4 session where members of the public are free to come up and
5 ask questions of any of the panel members and speakers
6 today.

7 There being no questions, the open public hearing
8 session is now closed. We were scheduled to have a guest
9 speaker. There has been a glitch in the technology at this
10 point so we are going to hold off on that now and we adverse
11 event going to break for lunch early. I would ask if
12 everyone can be back in the room a little ahead of schedule,
13 at one o'clock rather than 1:15. Thank you.

14 [Whereupon, at 12:00 noon, the proceedings were
15 recessed for lunch, to reconvene at 1:05 p.m.]

AFTERNOON PROCEEDINGS

1
2 DR. WILSON: I would like to welcome everyone
3 back. We are going to proceed with the agenda now. I would
4 like to introduce Dr. Joseph Curtis, who is the Senior
5 Biomedical Systems Engineer at the Marine Corp Systems
6 Command at Quantico, Virginia. Dr. Curtis is involved with
7 the development of environment monitoring devices for use
8 during warfare. These devices are not regulated by the FDA
9 and are not the subject of today's discussion, however, Dr.
10 Curtis kindly volunteered to provide information for these
11 devices. Dr. Curtis?

Guest Speaker

12
13 [Slide]

14 DR. CURTIS: At the Marine Corp Systems Command
15 they regulate a couple of high profile programs that some
16 of you may have heard about. One of them is called CBIR,
17 Chem-Bio Incident Response Force. We also have a variety of
18 teams that are specifically dedicated to responding to
19 incidences where weapons of mass destruction are present.

20 Many times, the marines have to go into
21 expeditionary environments where these weapons may have been
22 released. In an effort to try to protect the gentlemen, we
23 have developed a variety of technologies. We have suits
24 that actually protect them. We actually have gas masks and
25 now we are actually developing an actual individual sampler,

1 and this individual sampler is going to actually sample the
2 air space around any particular marine. This is very much
3 akin to the actual environmental monitoring technologies
4 that are already in place throughout the DOD and industry to
5 detect a variety of other types of substances.

6 [Slide]

7 The objective of the program is to provide the
8 Joint Force Commander with information that will assist the
9 warfighter in effectively exploiting the battlefield
10 environment while simultaneously protecting the forces
11 against exposure to chemical, biological and nuclear agents.

12 This particular program is an advanced concept
13 technology demonstration. It is actually a program where we
14 are actually going out and participating with industry to
15 capitalize on technology that is already available to try to
16 use to detect these types of agents. This particular
17 objective is to develop an environmental monitoring device
18 to sample the warfighter's exposure to these agents.

19 [Slide]

20 The DOD is very interested in a variety of
21 technologies. One of the things that they are interested in
22 is monitoring environment. Medical surveillance is what it
23 is all about. They want to encompass the periods before,
24 during and after deployment. To monitor an environment we
25 are looking for occupational and epidemiological threats and

1 diverse stressors. What is emphasized here is those that
2 are produced by chemical and biological nuclear weapons.
3 This is the top DOD objective that we are looking at.

4 The second one is the identification and
5 assessment of potential hazards and actual exposures to
6 environmental contaminants.

7 The GAO report recommends that there is a need for
8 enhanced low-level chemical warfare agent detection,
9 identification, and protection capabilities. These three
10 elements of doctrine are what is guiding this particular
11 program.

12 [Slide]

13 The National Academy of Sciences actually set up a
14 set of recommendations on this topic, and they recommended
15 that we develop technologies to detect and measure low-level
16 as well as high-level concentrations. The first priority is
17 development of improved passive sampling devices based on
18 existing technologies.

19 I am going to talk to you, guys, today about one
20 of our top technology candidates that we have, and it is a
21 passive sampling device. It does not require extensive
22 development because portions of it have already been
23 commercially available.

24 [Slide]

25 The approach to the program -- we are going to

1 focus basically on a demonstration that a commercial, off-
2 the-shelf passive sampling device will be available to
3 analyze and detect levels of bio and chemical agents
4 actually in the environment.

5 The second phase is to basically demonstrate that
6 we can actually collect the bio-weapon agents used in the
7 said technology. We also want to collect chemical weapons
8 and toxic industrial chemicals. Now, the chemical weapons
9 and toxic industrial chemicals, those are, unfortunately,
10 very pervasive threats when you go in some of the semi-
11 industrialized countries. For the topic of this discussion
12 today, we won't really focus in a lot on those; we will talk
13 about passive bio-weapon agent collection.

14 [Slide]

15 There are two pieces to the actual technology.
16 The first piece is based upon an aerosol sampling device
17 that will actually sample the actual air that is there and
18 actually concentrate whatever is actually in the air on an
19 actual substrate that will be a part of a modified
20 immunoassay. By combining these two technologies, we are
21 hoping to be able to develop an actual passive sampler that
22 is capable of monitoring environmental exposures, what the
23 individual warfighter is exposed to as he or she carries out
24 his duties actually in the actual warfare environment. Most
25 of the time, these individuals will be wearing protective

1 equipment to protect them against these agents. So, it is
2 not akin to the same types of problems that you all are
3 looking at with a person who is unprotected who gets exposed
4 and may have a clinical infection setting up. We are
5 talking about actually trying to monitor the environment
6 with a full complement of protective gear.

7 The analyzer unit uses light to detect what is
8 called UCP-labeled antibodies in a lateral flow immunoassay.
9 Dr. Henchal did talk a little bit today earlier about a
10 chromatographic assay. The chromatographic format assay is
11 very similar to that. The UCP is unconverted phosphor and
12 we will actually talk a little bit about that label.

13 As it is currently configured, it detects and
14 identifies biological materials. It is supposed to offer an
15 easy readout of many assays -- speed, relatively inexpensive
16 and the operational cost is low. We are hoping to have a
17 prototype available within eight months of the project
18 start.

19 [Slide]

20 Everybody here most likely is familiar with a
21 typical lateral flow immunoassay. The major portions of it
22 are the actual primary antibodies, then the actual
23 antibodies that will actually be labeled that actually
24 capture your analyte. So, you basically have a sandwich
25 assay that is available. You actually have it packaged in

1 an actual plastic cassette.

2 These can be massed produced very easily, very
3 quickly, and used in combination with the actual aerosol
4 detector. We are hoping to be able to provide the
5 warfighter in the field a rapid detection opportunity.

6 [Slide]

7 UCP -- this unconverted phosphor, this particular
8 particle here, you can actually go ahead and actually coat
9 this with a variety of substances that will allow you to
10 actually attach the antibodies of choice to it. These
11 antibodies can be specific for any particular antigen that
12 you are interested in. The antibodies that have been used
13 for the format at this present time have been supplied by
14 the Chemical Reagent Program. You have the actual
15 antibodies, your actual antigen, primary antigen, you have a
16 sandwich assay. The UCP reporter comes in a variety of
17 colors. That way, you are able to identify a broad spectrum
18 of actual antigen targets.

19 [Slide]

20 SRI is a company who has actually been contracted
21 to put together these assays. They are also one of the
22 prime candidates for our advanced concept technology
23 demonstration. They have basically reined the UCP
24 technology for use in this assay.

25 The phosphor microspheres are coated with silica

1 and these are used as labels or reporters in sandwich
2 assays. These antibodies can be conjugated to the silica
3 surface at optimal densities using standard cross-linking
4 chemistries. So, it is not very expensive.

5 The resulting functionalized phosphor particles
6 are then used to label captured target antigens with a
7 unique phosphor color assigned for each different antigen.
8 That is how you can detect a variety of agents in one assay.

9 [Slide]

10 Typical lateral flow assay format -- sample
11 injection port; the flow of the assay goes this way. You
12 can actually get one, two, three targets in this particular
13 configuration. There is control site calibration and
14 registration site that allows you to actually be able to
15 quantitate the level of antigens that are there and to
16 determine whether or not your assay is functioning
17 correctly. This is the actual illumination window where you
18 actually get your phosphorescence.

19 [Slide]

20 Assay sensitivities of the lateral flow
21 immunoassay -- these concentrations correspond to greater
22 than zero dose signal plus two times the standard deviation.
23 So, that is how we were able to go ahead and get this. This
24 information was provided to us by the actual manufacturer of
25 the assays. As you can see, we can get from picogram

1 levels, 100 spores with a variety of various targets,
2 Yersinia pestis, Bacillus globigii, mouse antibodies. We
3 can identify a variety of actual substances using this assay
4 format.

5 [Slide]

6 The future directions of the program, if it proves
7 successful, are to identify other candidate technologies
8 that can non-intrusively detect and measure individual
9 exposures at subclinical levels from environmental samples.
10 Hopefully, develop a regulatory strategy with options that
11 promote rapid development of candidate technologies where
12 necessary. Then, to transition this technology to
13 acquisition and fielding to the warfighters as rapidly as
14 possible.

15 The biggest problem that we are having is
16 overcoming the actual aerosol and deposition onto the actual
17 assay format itself, the actual paper. There is a variety
18 of uses for this technology right now. It is used
19 extensively. You will find that the literature is replete
20 with references for these organisms, for dust mites. A lot
21 of people are allergic to dust mites and you find that these
22 actual assays -- this combination of technologies, aerosol
23 capture, immunoassay is used to actually quantify the level
24 of dust mite antigens that are present in the environment.
25 A variety of other uses have been used to actually

1 quantitate pollen. Another assay use has been to quantitate
2 environmental hazards that are actually in the environment.
3 The combination of the actual aerosol capture and
4 immunoassay format is being used widely in the occupational
5 medicine and environmental monitoring arena, and we are just
6 trying to take and bring that same combination to a format
7 that we can use to outfit our actual troops in the field to
8 try to get an early step-up on identifying what is out
9 there. Thank you very much.

10 DR. WILSON: Thank you. At this point I would
11 like to move to the open committee discussion on the issue
12 for today. This portion of the meeting is open to public
13 observers, however, public observers may not participate
14 unless requested by the chair.

15 **Committee Discussion**

16 At this point, I would like to ask someone from
17 FDA to put the first question up. I would also like to
18 comment that there are no primary reviewers for issues
19 meetings. So, none of the panel members will have any pre-
20 prepared questions for this part of the discussion.

21 We can begin by either beginning to answer these
22 questions, or discuss the questions on the panel, or panel
23 members can certainly put forth other questions that they
24 may have thought of, other concerns. Dr. Specter?

25 DR. SPECTER: In looking at the first question,

1 part (a), the thing that comes to my mind that somewhat
2 corollary to that is when we go to consider all of this
3 should we be looking at all tests similarly, or should we be
4 looking differently at tests that would be designed as
5 primary screening tests versus those that are confirmatory
6 tests, especially as it pertains sensitivity, specificity
7 considerations? Obviously, in a screening test it is going
8 to be much more important to consider sensitivity for
9 something that shouldn't be in the environment versus
10 something you want to confirm and make sure it truly is what
11 you thought it was.

12 DR. WILSON: Anyone have anything they want to add
13 to that or any clarifications? Dr. Henchal, Dr. Meyer, any
14 comments about that?

15 DR. MEYER: The only comment I would have is that
16 personally I would like to see any test, whether it be used
17 as a screening test or rapid test or confirmatory test,
18 meeting the same criteria. So, what we hope to accomplish
19 with the rapid test is that they are very high confidence
20 level tests and you hold them to rigorous specifications.

21 DR. WILSON: Dr. Nolte?

22 DR. NOLTE: Just as sort of, I guess, a follow up
23 on that, I mean, what I have heard today is that these
24 systems may not be a single test system but a variety of
25 different approaches to identifying the same pathogen. So,

1 it is a little different situation if we are talking about
2 what the FDA might require of a stand-alone test versus
3 something that involves several different approaches, all
4 designed with the same aim, at identifying particular
5 biological agents. So, could you help me understand a
6 little bit better where we are going with this?

7 DR. MEYER: I was hoping that you would help me.

8 [Laughter]

9 DR. WILSON: Dr. Gutman, could you help us with
10 that?

11 COL. HENCHAL: At least from a DOD point of view,
12 or my own I should say, certainly what you said is true. I
13 think we are talking about a system of diagnostics first.
14 Again, I use the model that we used in the early days of HIV
15 of having two-test systems and, certainly, what would be
16 required under that case I think is the requirement that in
17 the labeling information it is explained about what is the
18 follow-on testing that would have to be done to confirm any
19 particular result.

20 I think also I should mention that Dr. Ted
21 Hatfield, who is here from the FIP, reminded me that if we
22 demand a certain high sensitivity for our screening assays,
23 that is going to lead very possibly to an increased number
24 of false positives that we are going to detect. So, follow-
25 on confirmation is actually going to be very critical.

1 DR. NOLTE: Again, just to help me, do you see
2 putting a single test for a biological agent in the
3 laboratory hands or a multiple test for that same agent? I
4 mean, you must have thought it through this far.

5 COL. HENCHAL: Multiple tests, yes.

6 DR. NOLTE: That is what I was trying to get at.
7 And, that sort of addresses some of Dr. Specter's question
8 because now you are not talking about individual test
9 sensitivity and specificity but you are talking about the
10 whole system together. So, you could have a high sensitive,
11 low specific test as the first line as long as a component
12 of that test system you had something that would be a
13 supplemental or a confirmatory test.

14 DR. SPECTER: Yes, that was exactly the point I
15 was making. If you are going to have a system that is
16 designed that way, in setting up approval for use of that
17 system do you use the same criteria when you know you want a
18 first test that is going to have a higher sensitivity and a
19 second test where you are sure the specificity is good.
20 That is actually what I would like to see addressed, that
21 is, do you look at them the same or do you look at them
22 differently? They have different purposes and,
23 consequently, you may want to look at them differently.

24 DR. MEYER: Well, for the rapid tests I feel that
25 we need to focus mostly on specificity. I think that is the

1 most important issue out of sensitivity/specificity. We
2 want to make sure that if that test detects something it
3 really is that agent.

4 DR. NOLTE: The conventional wisdom would be that
5 a screening test has high sensitivity but suffers a little
6 bit on the specificity part.

7 DR. MEYER: Yes, normally, but I think in this
8 scenario you have to remember that if something occurs
9 people are going to want an answer as rapidly as possible.
10 So, we take it out of the realm of science into a realm of
11 many, many different individuals knocking on our door,
12 saying, "what is it? Do you have an answer yet? What is
13 it? What is it?" And, if we do come up with a rapid answer
14 we want to be able to say with a high degree of confidence -
15 - yes, follow it up with a confirmatory test, but say with a
16 high degree of confidence that we have this particular
17 agent.

18 COL. HENCHAL: I think it is very likely that
19 future diagnostic systems will be looking for independent
20 markers almost simultaneously. Certainly, the platforms are
21 being built now that can allow gene amplification and
22 antigen detection on the same platform and, certainly, with
23 a process manually that we do at USMRIID we begin
24 immunodiagnosis at the same time that we do gene analysis.
25 So, it is possible to have a screening component as part of

1 the algorithm but it is very likely that the final system is
2 going to have almost simultaneous detection of more than one
3 marker at the same time.

4 DR. WILSON: Dr. Baron?

5 DR. BARON: If we talk about safety in terms of an
6 in vitro diagnostic device, what we are really talking about
7 is the implications to humans of false-positive and false-
8 negative results because it is not implantable; it is not
9 injectable. So, it has to do with the implications and in
10 this case what you are saying is that you would rather have
11 a false-negative result than a false-positive result because
12 you want to be specific. Is that what you mean?

13 DR. MEYER: That is a difficult question to
14 answer. Yes, I am going to say yes to that but, again, what
15 we are primarily interested in looking at is going to be a
16 specimen from a patient and is going to be background
17 information coupled with that.

18 DR. WILSON: The first question is broken into
19 four parts. One thing that we have been asked to help CDC
20 and Department of Defense with is the four different types
21 of specimens that will be tested. What types of data and
22 information are considered appropriate to evaluate the
23 safety and effectiveness? Can we apply the same criteria to
24 all of these or do they need different criteria? Let's see
25 what the panel has to say about that.

1 DR. BARON: Well, I certainly think you have
2 different criteria once you have a colony isolated on a
3 plate because you have the expertise of the microbiologist;
4 you have the type of medium on which the organism has grown
5 to focus you much closer than when you just have, say, an
6 organism recognized on a Gram stain or a specimen from a
7 patient with pneumonia. Do you know what I mean? I think
8 the criteria for a test at those two different levels are
9 very different. Don't you, guys, agree?

10 DR. NOLTE: Was the question about different test
11 methodologies or different specimens?

12 DR. WILSON: The question is what data, what
13 information do the developers of these tests need to
14 evaluate whether these devices are safe and effective, and
15 the four different categories are given. So, what will they
16 need to go out and develop products that we know are safe
17 and effective? So, if they are going to be different, and
18 one can make a reasonable case that they should be
19 different, then how do they differ? In other words, how
20 would the data and information to support safety and
21 efficacy -- what would those data really be?

22 DR. BARON: Well, let me give you an example of
23 what I am saying. Say, we are looking at a particular gene
24 or an organism and we know that that is an aerobic organism,
25 if we amplify that gene from a patient specimen there might

1 be gene present in anaerobic bacteria that would never grow
2 on the aerobic plate at all. So, you have to have a much
3 larger series of specificity tests at the specimen level
4 than you do at the culture identification level.

5 DR. WILSON: Dr. Ng?

6 DR. NG: I would like to bring up the things that
7 I would like to see from the clinical laboratory perspective
8 -- different specimen types, matrix effects, concentration
9 variables, cross-contamination, normal bacteria that could
10 interfere.

11 DR. MEYER: To address that, in our assay in
12 development, both the antigen detection and the molecular
13 assay development, what we are doing is not developing the
14 assay on purified cultures. We are using clinical matrices.
15 So, for example, all of our antigen detection assays were
16 developed with the background of human serum. We use human
17 serum as a matrix and we spike that with the bugs, and then
18 we go through the testing. For molecular assays we are
19 doing the same thing. We are creating the most appropriate
20 clinical specimen, spiking that, and then going through the
21 assay with that material.

22 The question is, I think, for proper validation
23 how many clinical specimens do we need? For example, do we
24 need to validate an assay that we put together for each type
25 of clinical specimen, number one? And, do we need to

1 validate an assay if you are using a different piece of
2 instrumentation for that assay?

3 DR. BARON: Yes. I don't think, for example, if
4 you would never receive a urine in the laboratory to test
5 for a particular pneumonic type disease that you validate
6 urine.

7 DR. MEYER: Right.

8 DR. SPECTER: Can I raise a question?

9 DR. WILSON: Yes, go ahead.

10 DR. SPECTER: I will address it to Steve directly.
11 Dr. Gutman, the questions that are listed here, are we
12 asking these questions uniquely, or are we asking these
13 questions as what do we need to do differently from the
14 standard?

15 DR. GUTMAN: Yes, I think we are looking for an
16 answer. We are pretty comfortable with evaluating usual
17 microbiology agents. So, I think it would be most
18 instructive if you would look at the hardest case scenarios.
19 I mean, I really think you should try and walk through
20 question number one and give us whatever pearls or insights
21 you have, but it is what is different or what is hard about
22 these because of the access to the usual samples. In the
23 background of what you are discussing is that we don't have
24 a particular preconceived notion about a particular level of
25 either sensitivity or specificity, and when we look at a new

1 product we determine whether it is safe and effective for
2 the claim, or if we are looking at a new product that it is
3 as safe and effective as a previous claim. So, you get what
4 you get and you decide if it is appropriate or not.

5 But everything is driven by intended use. If you
6 intend to use the product alone to decide you are not going
7 to treat a patient further, that is the intended use to rule
8 out disease. If you are using two tests together, frankly,
9 that is the intended use; it is a combination of the two
10 tests. If you are using four tests together, that is the
11 intended use. Everything is in the context of the planned
12 intended use in our data analysis. Se don't usually get two
13 or three tests together but there are instances where there
14 have been combinations or when one test has been labeled
15 based on cultures and expected follow up or on a second
16 serologic test as an expected follow up.

17 But I am not sure that we wouldn't profit by any
18 wisdom that you have in terms of just the general way we
19 approach these, but the reason we brought this to panel is
20 we thought there were unique issues with this particular
21 type of product.

22 DR. SPECTER: If I can continue, the unique issue
23 really is the non-availability of classic specimens that you
24 would find in routine testing. So, what we don't want to do
25 today is debate how the FDA goes about validating things;

1 what we want to debate is what we need to do when you don't
2 have sufficient materials to do what we would normally do.

3 DR. GUTMAN: That is exactly correct -- any advice
4 you have on surrogate data sets, minimum data sets or
5 appropriate labeling.

6 DR. WILSON: It would seem that the one exception
7 to that though is 1(a), the culture isolates because
8 certainly you could work with tests in an in vitro setting
9 where you could have plenty of specimens to work with and
10 refine your tests for that purpose. So, I think that is
11 probably very similar to anything else. I think it is when
12 you get into i(b), (c), (d) and the other questions where we
13 enter an area where this is considerably less information.
14 Given that there will never be, hopefully, a clinical trial
15 for the use of these, the question is what do they need to
16 do to validate that these tests are safe and effective? As
17 has been mentioned in several conversations throughout the
18 day today, there are significant implications to calling a
19 false positive as well as a false negative with these tests.
20 So, any guidance that the panel members can give is really
21 what they are looking for today.

22 DR. BARON: Well, I actually disagree with
23 something you just said because, for example, Legionella --
24 if you grow Legionella in culture it is really nothing like
25 the Legionella that you get out of a first sputum from a

1 patient with Legionella pneumonia, and I think that is true
2 Yersinia pestis as well. Certain genes are turned on in the
3 human and turned off the minute they come out. So, I think
4 that is a problem that you have to deal with.

5 I would also like to make a point about animal
6 models. I did my doctoral thesis with mouse neutrophils and
7 in going in I thought they were the same as human but after
8 I studied them together in the laboratory I realized they
9 were radically different. So, I think the model that you
10 use has to be carefully chosen as well.

11 DR. MEYER: I agree with that, and that is why the
12 strategy for assay development is not dependent upon one
13 particular target, particularly for the molecular assays
14 where it is a panel that looks at plasmid markers and
15 genomic markers.

16 DR. WILSON: Dr. Hammerschlag?

17 DR. HAMMERSCHLAG: Even if the best molecular
18 methods theoretically could detect one set of DNA/RNA, but
19 in reality, for instance even with tests that we have out
20 there on the market right now -- there are a number of kits
21 for Chlamydia trachomatis and for Neisseria gonorrhoea and
22 how they performed in the research laboratory involved in
23 the large clinical trials is one thing, and when they got
24 into the clinical laboratory they had a lot of problems with
25 reproducibility. There was a recent paper in The Journal of

1 Clinical Microbiology that dealt with that.

2 I am interested in C. pneumoniae and there was a
3 recent study that is going to be presented in the meetings
4 in Helsinki about the issue of use in tissue, in this case
5 vascular tissue, where specimens were sent around -- this
6 was organized in Vienna and there were nine different labs
7 using nine different assays. When they sent around the
8 spiked specimens the correspondence was very good. When it
9 came to the actual tissue it was all over the place. So,
10 you have this problem even in the lab. I don't think you
11 can really come up with a surrogate situation because,
12 again, every specimen is different. I get the question a
13 lot about the clinical use of Chlamydia tests -- "oh, we can
14 use it in urine in adults in women and men for Chlamydia
15 trachomatis, why can't we use this in prepubertal children
16 suspected of sexual abuse?" Of course, that is an issue
17 where a false positive would be devastating.

18 But I think the only way out of this is multiple
19 tests, and you have to assume -- I don't even think two
20 would be enough. I think you would probably have to have
21 three and then you would have to set up a series of criteria
22 as to what combination etc. would be necessary because I
23 think this is a situation where you want to get the best
24 sensitivity and specificity.

25 DR. DURACK: Clearly, the movement is towards the

1 likelihood of using multiple tests. Col. Henschel, you
2 mentioned the analogy of the early days of HIV where you had
3 two tests, and that kind of implied a mini-panel of two but
4 actually it is a screening test and a reflexive test. So, I
5 think we need to think of that distinction, whether we are
6 using a panel which is applied all at once and then
7 analyzed, or whether we are using a series of reflexive
8 tests. And, we can't answer that until we know the
9 characteristics of the available tests.

10 I feel we are at a very early stage of this, and
11 if you have five viable tests you have to analyze the
12 performance characteristics of each one, and then decide
13 whether you will use three of them in a panel that is
14 applied simultaneously or whether you will use one of them
15 followed by two in reflexive testing, or whatever. Until
16 you have the test in front of you and you do the performance
17 characteristics you won't be able to answer the question.

18 To give you a pretty simple example, if you think
19 about tests on CSF for meningitis, they tend to be rather
20 poor tests but you only have to put three or four of them
21 together and you come up with a very good combination. And,
22 that is not reflexive testing. We do the CSF tests as a
23 panel and put them together either mentally or in a
24 computer. So, I feel we have a long way to go with taking
25 all the viable tests and establishing performance

1 characteristics before we can answer the question.

2 DR. WILSON: Dr. Hawkins?

3 DR. HAWKINS: Would we not assume, because this is
4 time critical, that the tests will be done as a panel?

5 DR. DURACK: We think it will be multiple tests
6 but whether it will be a reflexive series, and a reflexive
7 series might be done very quickly, in a matter of minutes,
8 or it might be done in a matter of minutes and then hours,
9 or minutes, hours and a day, or something like that but we
10 don't know yet whether it will be that or five things on a
11 strip.

12 MR. REYNOLDS: One question that I have, you
13 mentioned the false positives and false negatives, and that
14 is fine if we are talking about the test being done in the
15 public health lab or a higher-tier lab. Again, as Dr.
16 Specter mentioned earlier, if it is done at an entry level
17 lab, where you only have one patient coming in or two
18 patients and you have a Gram-positive rod -- is it anthrax
19 or is it not anthrax, all I want to do is rule out -- and
20 they make a mistake there, you know, at that level you may
21 miss a very early case and a potential outbreak or a
22 potential BT event. So, one of the other questions you have
23 to consider is who is going to be using this test. You
24 know, are we talking about something being done at a level C
25 or D lab, or are we talking about something being done in a

1 level A lab?

2 COL. HENCHAL: In the case of a real bioterrorism
3 event, and again I refer back to Dr. Ted Hatfield who
4 reminded me of this, we probably are not going to be dealing
5 with just one patient or two patients and actually whether
6 or not there has actually been an incident will probably be
7 based on a lot of specimens at one time.

8 I mean, we certainly imagine the case of a true
9 bioterrorism WMD event, and there are going to be a lot of
10 patients and it is probably going to be the sum of all those
11 that is going to point to an actual event.

12 DR. NOLTE: I think one of the points that Mr.
13 Reynolds is making is that there may be a lot of patients
14 but the concentration of them may be such that at any one
15 laboratory -- you know, the analogous situation is you have
16 a food point outbreak of disease, and unless there is
17 somebody collecting data and analyzing that any one
18 laboratory may see only one or two cases and not notice an
19 increase in disease.

20 COL. HENCHAL: And this is going to be an
21 important consideration for kind of the network that CDC is
22 putting together so that we really are able to look at real-
23 time collection of data; that we have a good reporting
24 system because it might be the one or two cases scattered
25 across an area that are going to tip you off, I would think.

1 Isn't that true?

2 DR. MEYER: Yes, that is very true. Also, couple
3 with that is the fact that it goes beyond laboratory
4 diagnostic tests. It gets into surveillance issues, and
5 there is a major effort right now going on in pulling
6 together a system whereby there is reporting by hospitals,
7 for example, of unusual cases showing up, and a
8 communication network that is being put together, and this
9 all gets coupled with the lab analysis as well.

10 DR. WILSON: Dr. Baron?

11 DR. BARON: Well, that is why I would argue that
12 at your first level labs sensitivity should be more
13 important than specificity because if five different
14 laboratories see an organism and rule it out you won't get
15 that first alert, if there are five different labs in five
16 different parts of the country.

17 DR. WEINSTEIN: I guess I have sort of a similar
18 question as to point of care testing versus the type of
19 testing that would be done in a more controlled laboratory
20 environment, and whether you should have different criteria
21 for sensitivity and specificity in the point of care
22 situation as opposed to the most controlled, higher-tier
23 laboratories.

24 COL. HENCHAL: My attitude about this, and we have
25 been talking a lot about this because we have a need for

1 point of care devices in the military -- my philosophy about
2 this is that the point of care analysis test is really there
3 to help the physician make a decision on the best choice
4 when he is faced with this problem, ultimately, the clinical
5 signs and symptoms that he observes, that he is going to
6 make his decision upon and the point of care test is really
7 there not so much to make a diagnosis but to increase his
8 level of suspicion, his index of suspicion that maybe a WMD
9 agent is involved in this particular incident. I think that
10 history would say that the physician is going to begin
11 treatment based on his observation of symptoms and not
12 necessarily directly on a point of care assay.

13 DR. MEYER: I think also we are talking about
14 different types of possible scenarios. In the case of an
15 overt release and announcement of an agent, level A labs are
16 not going to be totally involved. It is going to be
17 immediately ramped up to the whole network. In the
18 situation where there is a covert release, that is where you
19 have the little sprinkling of cases coming in here and there
20 and that is a different scenario. There is a lot of
21 awareness right now in level A laboratories -- you have to
22 remember that with level A labs we are talking basically
23 about hospital laboratories and how many there are across
24 the country. So, there is a concerted effort right now to
25 raise the level of awareness so that when these labs get an

1 isolate of something there is a thinking process that goes
2 on to say, well, we need to check this further.

3 DR. WILSON: Dr. Nolte?

4 DR. NOLTE: It does bring one back to 1(a) and
5 the point that you just made. I mean, the conventional
6 culture identification methods are pretty well established
7 for these bioterrorism agents and my threshold for
8 skepticism about a conventional biochemical test and how
9 well it would work would be much less than it would be if it
10 progressed up the technology tree, if you will, where there
11 is less information known about the different gene targets
12 and that sort of thing. So, I guess there is another level
13 of complexity to this that I don't know is reflected in
14 those questions, but I guess what I am saying is if you came
15 with a panel of biochemical tests that would be required to
16 identify the ten most likely bacterial agents and tried to
17 sell that to the FDA, I don't think there would be a lot of
18 data that would be required that isn't already available.

19 DR. MEYER: Right.

20 DR. NOLTE: If it were a nucleic acid based test
21 to identify these agents directly in a clinical specimen,
22 then we are going to be a little bit more demanding, I would
23 think.

24 DR. MEYER: Yes.

25 DR. NOLTE: I think what we are talking about is

1 getting the kind of testing into the hands of the people
2 that are going to be the first alert or the first
3 responders, whatever the right term is, you know, the things
4 that labs already have experience with, and that would
5 probably boil down to some sort of conventional, you know,
6 metabolic panel or biochemical panel, and that would be
7 where I would want to spend my money, and then work on the
8 other things higher up in your chain of command, or
9 whatever, in terms of laboratories. Am I thinking about
10 that appropriately, experts?

11 COL. HENCHAL: Yes.

12 DR. MEYER: Yes, just to give you another
13 scenario, the thing that I think is important to remember is
14 that in many cases what we are talking about is a clinical
15 situation where there is some clinical evidence or suspicion
16 of something but basically we have an unknown because a lot
17 of these agents initially present with the same types of
18 symptomatologies. So, we have an unknown situation and we
19 need an answer as rapidly as possible.

20 The tests that we are talking about in development
21 or validation are what we hope will give us that answer.
22 What is going to be followed up with this within a matter of
23 hours of an answer is a conventional microbiology test to
24 follow up and confirm that, and all the other ancillary
25 tests that go into this.

1 DR. NOLTE: What we are going to be faced with in
2 1(a), I mean, in a hospital based microbiology lab the thing
3 that we are likely to find is a positive culture. Once we
4 have that culture in hand, having the appropriate tools to
5 determine definitely whether it is B. anthracis or
6 Francisella tularensis and do that quickly would be useful
7 and it would be something that wouldn't be a big
8 intellectual leap in terms of having the kind of supporting
9 information that you would need.

10 DR. DURACK: Just coming back to Dr. Weinstein's
11 earlier question about whether there should be different
12 criteria or different levels, I think it is inevitable that
13 there will and it is a matter of prior probability because
14 if Dr. Baron walks into her lab first thing in the morning
15 and the question is, is this anthrax, the answer is the
16 prior probability is extremely low that this will be
17 anthrax. By the time it gets to Dr. Meyer, the prior
18 probability that this Gram-positive is going to be anthrax
19 has gone way, way up. That means that whether we like it or
20 not there will have to be different criteria between the
21 level A lab and going up the ladder. And, that is okay. I
22 mean, traditionally, as you were getting at earlier, the
23 screening testing is the more sensitive and the final test
24 is going to be the more specific. So, we might wish for the
25 specificity at the beginning; I don't think we are going to

1 be able to get it on the basis of prior probability. We can
2 put together a lot of rare events and come up with an answer
3 that shows multiple exposures, of course, even with a test
4 of sensitive and not very specific.

5 DR. BARON: Given the kinds of testing methods
6 that you are currently working on, which I think is what you
7 came to us for advice on, I think what we are talking about
8 is an announced bioterrorism event and a bunch of patients
9 who have some symptoms or who have no symptoms yet and you
10 want to be able to ramp up very quickly a test for a series
11 of people and see if what you think it is, is what it is, or
12 in a panel of ten things, which one is it. That is what you
13 are really asking for advice on, not that other stuff, I
14 think. Is that correct? Because that is what you are
15 working on now.

16 DR. MEYER: Yes.

17 DR. BARON: So, then you are absolutely right.
18 Specificity is much more important than sensitivity. Matrix
19 is very important so you need an animal model because you
20 are not going to put it in a bunch of people. So, you
21 already have the closest animal model, those monkeys I
22 guess. So, how many monkeys are you going to do?

23 DR. MEYER: We don't have the monkeys; Col.
24 Henchal has the monkeys. That is correct. The other thing
25 is that the way I see it is that we tried to create the

1 natural situation as best as possible, or the real specimen
2 scenario as best as possible. So, using plague as an
3 example, Yersinia pestis testing, and after initial exposure
4 the most common specimen would most likely be a tracheal
5 wash or sputum. So, we try to create that situation by
6 basically spiking saliva as a surrogate and then doing our
7 sample prep and testing on that material, and we look at
8 different levels of spiking in that type of material.

9 DR. BARON: Yes, and then you can validate it with
10 a few animals because, as I said, what you are looking for
11 in the spiked sample may not be the antigens or the organism
12 expression in the disease state.

13 DR. MEYER: Right, yes.

14 DR. BARON: Certainly, if I were a biological
15 warfare developer I would work real hard to make my agent be
16 transparent to your test.

17 DR. MEYER: Sure. Right. Yes, and the animal
18 system certainly will help but, as you realized, that still
19 in an of itself is not definitive because the real scenario
20 is coming out of the human.

21 COL. HENCHAL: Thank you for really opening the
22 discussion to an issue that is particularly important to us,
23 and that is we do have some animal models but they are not
24 perfect and in some cases they only roughly approximate the
25 human illness. I sit and ask this question very frequently

1 about how well are we going to be able to use these animal
2 models to mimic the human clinical disease to get the range
3 of values that we need for diagnostics? So, I am interested
4 in your opinion in what we might even have to do to validate
5 the animal models that we want to use for certain agents.

6 DR. SPECTER: I think part of that process would
7 deal with paralleling specimens, and they may have to be
8 spiked specimens statistical human serum versus the animal
9 specimens and you can test those in parallel.

10 Another point I wanted to bring up, going back to
11 this issue, is that it sounds to me that we have talked
12 about two very, very different scenarios. One is where an
13 agent has been used and a few people have been infected, and
14 you are very concerned about the diagnosis of infection for
15 those individuals. The other scenario is the weapon of mass
16 destruction where your concern is far greater for the public
17 health. In that particular scenario sensitivity is all that
18 matters because, quite frankly, if you have lots of people
19 sick and you have a sensitivity test with some sacrifice of
20 specificity, you are not going to worry about the
21 specificity right away because you are going to see lots of
22 sick people turning up positive with this. So, the
23 sensitivity is the key issue here, again, in the screening
24 test. You can then rule out the six or seven people that
25 you picked up that were false positives, with the

1 confirmatory test, within a day. But the real issue is if
2 you are worried about a weapon of mass destruction and
3 getting help for the public welfare, then the key is finding
4 out does it exist because the probability is zero for almost
5 all of the agents you are talking about, except for one
6 which I can give you a beautiful scenario for, and that
7 would be influenza. If somebody were to create a super-
8 influenza and introduce it during flu season, it would drive
9 you absolutely nuts.

10 DR. MEYER: I agree with you a hundred percent. I
11 take the attitude of we have to strive for both sensitivity
12 and specificity and end up where we end up. I mean,
13 certainly in test development we look at how specific can we
14 be as well as how sensitive we can be, and keeping those in
15 balance.

16 DR. SPECTER: Just to take that a little bit
17 further, if you are talking about a weapon of mass
18 destruction you need something that is 100 percent
19 sensitive. Now, if you can do that and you can get the
20 specificity up, well and good, but the point is that with an
21 agent like this where you are talking about a potential
22 devastating consequence, you need 100 percent sensitivity
23 and you have to sacrifice the specificity to make sure that
24 in that kind of scenario. If you are talking about the
25 covert situation with a few sick people, that is a different

1 scenario.

2 DR. WILSON: Dr. Hawkins?

3 DR. HAWKINS: I disagree with that completely. If
4 you have a terrorist incident what you lose on the
5 sensitivity for a single individual you will pick up in that
6 there will be so many individuals presenting.

7 DR. SPECTER: Yes, but you want to get the first
8 case as quickly as you can.

9 DR. HAWKINS: With bioterrorism you are going to
10 have thousands of them.

11 DR. MEYER: Yes, that is true but I think the
12 caveat to that is that you also want to make sure you
13 identify the correct agent.

14 DR. SPECTER: So that is specificity.

15 DR. MEYER: Right.

16 DR. SPECTER: But when you are in a scenario where
17 you have zero incidence and these agents are very different
18 -- I mean, you are not going to mistake plague for small
19 pox, for example, which have very different approaches to
20 treatment, and it is unlikely you are going to mistake
21 plague for a Staph. infection either. So, my concern is
22 does it exist? Is it here? And, do we need to take rapid
23 action? And, that is why I believe the sensitivity is much
24 more of an issue than the specificity. Then you can sort
25 out with a more specific test.

1 DR. WILSON: There are a couple of themes I think
2 that have emerged that might help you in terms of developing
3 the tests: sensitivity and specificity are both important
4 for different reasons and, as Dr. Nolte said, the standard
5 as you move down from 1(a), (b), (c) and (d) will probably
6 become more difficult for you guys to meet. It would seem,
7 for one thing, that you can work with at this point -- given
8 that you won't have a human model and animal models may be
9 problematic -- you can work with culture isolates. I agree
10 with what Dr. Baron said, they may not be identical but at
11 least you would have something to work with.

12 I think the first order of business would be to
13 make sure that your assays are as perfect as possible
14 against known isolates and that there is no cross-
15 contamination, because until you do that you wouldn't have a
16 lot of confidence to move to the next level and the next
17 level after that. So, I would think that that would be the
18 first thing that you would have to provide to satisfy the
19 FDA.

20 I think that as you move down it is going to
21 become increasingly difficult for anyone to design data that
22 will satisfy anyone around this table because you are just
23 going to be working in an unknown arena, but at least if we
24 know the foundation is there we would have a lot more
25 confidence. Dr. Durack?

1 DR. DURACK: Just one further point about animal
2 models, which I have been interested in for years. They are
3 often criticized on the basis of, well, they are different
4 to humans but this is missing the point of where the animal
5 model can really contribute. It is useful for comparing
6 tests. Allowing that it is different from humans, you can
7 still use it in your hierarchy of specimens that you
8 mentioned to make a big step in comparing which tests you
9 will go forward with, and that is even allowing for the fact
10 that it is quite different to humans in one way or another.
11 So, I think I agree with Dr. Baron that animal models will
12 be essential at least as you go through the hierarchy of
13 specimens.

14 DR. WILSON: I just want to make one other comment
15 about the issue of specificity. In addition to the public
16 consequences of an event such as this in terms of how the
17 public would perceive this, the accuracy of these tests is
18 extremely important, as you know, in terms of what events
19 follow. During the top-off exercise in Denver, when you
20 call for a push-pack from the national pharmaceutical
21 stockpile you don't want 500,000 doses of the wrong drug
22 being shipped to you because, not only would you have to
23 send it back, it is not helping anyone. So, the issue of
24 specificity early on will be extremely important.

25 Also, the issue of specificity and timeliness

1 because, while you can't stop an outbreak, you may be able
2 to deflect the epicurve a little bit in the right direction
3 if you have gotten a prompt response. So, it seems that
4 you are going to have to have an extremely specific test as
5 early as possible.

6 DR. MEYER: Yes, that is a very good point.
7 Absolutely. I mean, that is why we need to know exactly
8 what the agent is because all of these resources and assets
9 that are going to be mobilized are based upon what the
10 answer is. So, that is extremely important.

11 The other point is that in many cases -- again,
12 getting back to the specimen being tested as an unknown, you
13 have to remember that we are testing against a number of
14 agents. So, we have a panel of various agents that we are
15 looking at, and we are looking for which one lights up, and
16 when that lights up we need to have a high confidence level
17 that that is a true positive.

18 DR. WILSON: Dr. Baron?

19 DR. BARON: So, then I would reiterate that you
20 need to be checking high numbers of organisms that are
21 likely to be in the matrix specimen, not forgetting
22 anaerobes or fungi or other things that might normally not
23 be tested in this situation because you don't have the time
24 to rule those out in a bioterrorism event. So, I would
25 broaden the number of potential conflicting agents to be as

1 huge as possible.

2 DR. MEYER: Yes.

3 DR. WILSON: Are there any other comments about
4 question one? Dr. Stewart?

5 DR. STEWART: A question I had sort of dealt with
6 a situation where perhaps, come some morning, you find three
7 men dead in one field unit, how are you going to approach
8 what specimens you are going to collect and test?

9 COL. HENCHAL: As I understand your question, you
10 are asking what specimens we are going to collect from the
11 deceased, from the discovered deaths?

12 DR. STEWART: Yes.

13 COL. HENCHAL: Actually, we do have a protocol for
14 that. My answer to that is we collect all the specimens
15 that we can. We have a protocol for swab sampling; for
16 taking tissues; for taking fluids; and autopsy materials,
17 and all that becomes part of the package for the unexplained
18 death. You have to because the number of agents that could
19 be involved is quite large and they all have a different
20 presentation in terminūs so that we do have to make the
21 diagnosis based on testing many different specimens from the
22 same source.

23 DR. STEWART: What level of protective gear are
24 your samplers of the dead going to be using?

25 COL. HENCHAL: That is another excellent question

1 and the protective gear that currently is standard in the
2 Army, at least, and was part of actually even post-
3 evaluation of the Desert Storm arena is the standard Army or
4 DOD MOP gear, the protective gear that includes a gas mask
5 and a full garment. That is now part of the doctrine for
6 the sampling teams when there is an index of suspicion of a
7 chemical or a biological event.

8 DR. BARON: That is a good point that Dr. Steward
9 brings up because once a body dies and decomposes the
10 organisms that are normally present in the bowel are present
11 in great numbers in places previously sterile. So, that is
12 why I think you need to look at all those organisms in large
13 numbers in your system.

14 DR. WILSON: Dr. Nolte?

15 DR. NOLTE: We were thinking about trying to
16 identify things that might be unique in terms of
17 requirements for this kind of situation, and although, you
18 know, we are well aware of the problems inherent with a
19 nucleic acid technology and false positives, with this
20 application, depending upon where you are in the tier, you
21 are extremely concerned about specificity so that I would
22 probably want to see lots of data on unspiked specimens and
23 the false-positive rate associated with the technology. I
24 think the previous comments have been more focused on the
25 biological cross-reactivities. I am more focused here on